AstraZeneca

Revised Clinical Study Protocol

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A Randomized, Double-blind, Parallel-group Study to Evaluate the Effect of BYDUREON Compared with Placebo on 24-hour Glucose Control in Metformin-treated Patients with Type 2 Diabetes

Sponsor: AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19809

AstraZeneca Research and Development site representative

[redacted]

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

PROTOCOL SYNOPSIS

A Randomized, Double-blind, Parallel-group Study to Evaluate the Effect of BYDUREON Compared with Placebo on 24-hour Glucose Control in Metformin-treated Patients with Type 2 Diabetes

Principal Investigator

[redacted]

Study site(s) and number of patients planned

Approximately 30 sites in the United States are planned to participate in this study.

Approximately 110 patients are planned to be enrolled in this study.

Study period		Phase of development
Estimated date of first patient enrolled	4th Quarter 2014	Phase IV
Estimated date of last patient completed	4th Quarter 2015	

Study design

This will be a randomized, double-blind, parallel-group study comparing BYDUREON® (extended release exenatide) once weekly (EQW) vs. placebo in patients with type 2 diabetes mellitus (T2DM) treated with metformin. The patient population will consist of male and female patients, age ≥18 and ≤75 years, inclusive, with T2DM who have inadequate glycemic control (hemoglobin A1c [HbA1c] ≥7% and ≤10% at screening) who have been receiving a stable dose of metformin (≥1500 mg/day) for at least 8 weeks. Approximately 110 patients will be randomized in a 1:1 ratio (EQW:placebo); to achieve approximately 55 patients per treatment arm. After the 4-week lead-in period, patients will be randomized and then treated for 10 weeks. Following 10 weeks of treatment, standard safety assessments will be evaluated during a 4-week follow-up period.

A continuous glucose monitoring (CGM) system will be used to measure the patient's interstitial glucose level. The 7-day assessment using the CGM will be performed during the

lead-in period (Day -8 to Day -1), and during the Treatment Period (Day 21 to Day 28 and Day 63 to Day 70). The glucose measurements used for assessment of the primary endpoint will be analyzed from the CGM data.

Objectives

Primary Objective:	**Outcome Measure:**
To compare the effect on 24-hour mean weighted glucose after 4 and 10 weeks of EQW plus metformin with placebo plus metformin, using data obtained by a CGM system	Change in 24-hour mean weighted glucose from baseline (Day -1/1) to Day 6 of Week 10 (Day 69/70) and to Day 6 of Week 4 (Day 27/28)

Secondary Objectives:	**Outcome Measures:**
To examine the intra-patient variability of the change in 24-hour mean weighted glucose at the beginning and the end of the dosing cycle (Week 10 of treatment in EQW patients), using data obtained by a CGM system	Change in 24-hour mean weighted glucose between Day 1 of Week 10 (Day 64/65) and Day 6 of Week 10 (Day 69/70) within each EQW-treated patient
To compare the effect on fasting plasma glucose (FPG) and 2-hour postprandial glucose (PPG) after 4 and 10 weeks of dosing of EQW plus metformin with placebo plus metformin	Change from baseline (Day 1) to Day 6 of Week 10 (Day 70) and Day 6 of Week 4 (Day 28) in FPG Change from baseline (Day -1) to Day 6 of Week 10 (Day 69) and Day 6 of Week 4 (Day 27) in 2-hour mean weighted PPG (after the breakfast meal)
To compare the following parameters after 4 and 10 weeks of dosing between the EQW plus metformin and placebo plus metformin treatment groups, using data obtained by a CGM system: the effect on 24-hour mean amplitude of glucose excursion (MAGE) the proportion of time patients who had plasma glucose measurements of: <70 mg/dL, ≥70 mg/dL and ≤180 mg/dL, or >180 mg/dL	Average of change in 24-hour mean weighted glucose from baseline (Day -1/1) to Days 1 to 6 of Week 10 and Week 4 calculated. (standard deviation, MAGE, “Distance travel”, “Energy”)
To compare the effect on HbA1c levels and 2-hour PPG after 4 and 10 weeks of dosing of EQW plus metformin with placebo plus metformin	Change from baseline (Day -1) to Day 6 of Week 10 (Day 69) and Day 6 of Week 4 (Day 27) in 2-hour mean weighted PPG (after the breakfast meal)

Exploratory Objective:	Outcome Measure:
The difference in daily 24-hour mean weighted glucose during Week 10, within and between treatment groups, will be assessed and described descriptively. In addition, qualitative similarities and differences in each treatment group in daily CGM profiles will be evaluated.	Exploratory statistical parameters like "Distance traveled", the arch length of this curve and the other measures of "Energy" will be calculated

Target patient population

The study population will consist of male and female patients, ≥18 years and ≤75 years of age, inclusive, with T2DM who have inadequate glycemic control (HbA1c ≥7% and ≤10% at screening) who have been receiving a stable dose of metformin (≥1500 mg/day) for at least 8 weeks.

Duration of treatment

This study consists of a 4-week lead-in period, followed by a 10-week treatment period. Following 10 weeks of treatment, standard safety assessments will be assessed during a 4-week follow-up period.

Investigational product, dosage, and mode of administration

During the treatment period patients will be randomized to 1 of 2 treatment arms:

- BYDUREON® EQW + open-label metformin XR (1500-2000 mg) or
- Placebo + open-label metformin XR (1500-2000 mg).

Double-blind study medication (EQW or placebo) will be administered subcutaneously once weekly (Day 7 each week).

Other treatment

After qualifying for entry into the lead-in period, patients will discontinue their current metformin therapy and begin a 4-week medical nutrition and open-label metformin XR lead-in period.

Statistical methods

Analysis populations

The Modified Intent-to-Treat (ITT) population will consist of all randomized patients who received at least one dose of randomized study drug. The Modified ITT population will be used for all efficacy analyses.

The Evaluable population will consist of all Modified ITT patients who completed the study and were in compliance of study procedures. The Evaluable population will be used to perform supportive analyses for primary and secondary endpoints.

Analysis of the primary variable

The primary endpoint of 24-hour mean weighted glucose will be obtained by a CGM method and calculated as the area under the curve (AUC) from the 24-hour glucose profile, divided by 24 hours. Details on AUC computations for partially missing 24-hour glucose profiles will be described in the statistical analysis plan. The changes in 24-hour mean weighted glucose from baseline (Day -1/1) to Day 5-6 of Week 10 (Day 69/70) and to Day 6 of Week 4 (Day 27/28) will be analyzed using a maximum likelihood-based mixed model repeated measures (MMRM) method. The MMRM model will include change in 24-hour mean weighted glucose as the dependent variable; treatment, HbA1c stratum (<8.5% vs. ≥8.5%), baseline 24-hour mean weighted glucose, week of visit, and treatment-by-week interaction as fixed effects, and patient and error as random effects. All post-baseline measurements (including early termination visits) of the 24-hour mean weighted glucose will be included in the analysis with no imputation of missing data other than that inherent in the MMRM model. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion. The least squares (LS) means, standard errors of LS means, and 2-sided 95% confidence intervals (CI) for the mean change within each treatment group and the difference between treatment groups will be presented. P values will be provided for the comparison between treatment groups. Data normality will be evaluated. If the data require logarithm transformation to meet the normality assumption for statistical modeling, the LS mean and the corresponding 95% CI will be calculated at the log scale, and the geometric mean ratio and its corresponding 95% CI will be calculated by taking the anti-log of the corresponding values within each treatment group and for treatment comparisons. The 2 primary endpoints will be tested sequentially (Week 10 comparison will follow by the Week 4 comparison) and the family-wise Type I error will be controlled between primary and secondary endpoints.

Analysis of the secondary variables

Intra-patient difference and variability of the 24-hour weighted mean glucose between Day 1 and Day 6 of Week 10 will be calculated and presented descriptively; no hypothesis testing will be performed.

The change in FPG from baseline (Day 1) to Day 6 of Week 10 (Day 70) and Day 6 of Week 4 (Day 28), and the change in 2-hour mean weighted PPG (after the breakfast meal) from baseline (Day -1) to Day 6 of Week 10 (Day 69) and Day 6 of Week 4 (Day 27) will be analyzed using a similar MMRM model as the one described for the primary endpoints; except for the analysis of the endpoint of FPG, the baseline FPG will replace the baseline 24-hour mean weighted glucose as one of the fixed effects.

The change in HbA1c from baseline (Day 1) to Day 6 of Week 10 (Day 70) will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline HbA1c as a covariate.

In order to control the family-wise Type I error, a sequential testing procedure will be implemented. In the hierarchical testing order, the primary endpoints of 24-hour mean weighted glucose at Week 10 will be tested first, followed by 24-hour mean weighted glucose at Week 4, then the secondary endpoints: FPG at Week 10, 4-hour mean weighted glucose at Week 10, then FPG at Week 4, and 4-hour mean weighted glucose at Week 4.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	American Diabetes Association
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the 24-hour glucose curve
HCG	human chorionic gonadotropin
BID	twice daily
BMI	body mass index
CI	confidence interval
CGM	continuous glucose monitoring
CSA	Clinical Study Agreement
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ET	Early Termination
EQW	extended-release formulation of exenatide (BYDUREON)
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GMP	Good Manufacturing Practice
HbA1c	hemoglobin A1c
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
IP	investigational product
IRB	institutional review board
ITT	Intent-to-Treat
IVRS/IWRS	interactive voice response system/interactive web response system

Abbreviation or special term	Explanation
LS	least squares
MAGE	mean amplitude of glucose excursion
MMRM	mixed model repeated measures
PK	pharmacokinetic
PPG	postprandial glucose
PPGT	postprandial glucose tolerance
SAE	serious adverse event
SAP	statistical analysis plan
SBGM	self-blood glucose monitoring
Scr	serum creatinine
SD	standard deviation
SGLT-2	sodium-glucose co-transporter 2
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
TSH	thyroid-stimulating hormone
TZD	thiazolidinedione
ULN	upper limit of normal
WOCBP	women of childbearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Diabetes is a major public health concern globally and especially in the US. According to the US Centers for Disease Control and Prevention, nearly 29 million people in the US have diabetes (Centers for Disease Control and Prevention, 2014). Type 2 diabetes mellitus (T2DM) accounts for 90-95% of diagnosed cases of diabetes and is associated with older age, obesity, family history of diabetes, gestational diabetes, impaired glucose metabolism, physical inactivity, and certain ethnic groups such as African Americans, Hispanics, and American Indians. Diabetes is a leading cause of blindness, end-stage renal disease and non-traumatic lower limb amputation, and is a major risk factor for coronary artery disease and stroke (Miser, 2007). Interventions that improve glycemic control reduce microvascular complications involving the eyes, kidneys and nerves, and may reduce macrovascular complications such as myocardial infarction (American Diabetes Association, 2014; Bolen et

al, 2007). Currently, there are different classes of antidiabetic drugs available on the market and their selection depends on the nature of the diabetes, age, and situation of the patients.

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that exhibits many of the same glucoregulatory or glucose-lowering actions as GLP-1, a naturally-occurring incretin hormone. However, exenatide is not substantially degraded by dipeptidyl peptidase-IV, which efficiently degrades native GLP-1 in vivo (Kieffer et al, 1995). Exenatide has been shown to reduce fasting and postprandial glucose (PPG) concentrations via enhancement of glucose-dependent insulin secretion (restoration of first-phase insulin secretion [Fehse et al, 2005]), glucose-dependent suppression of glucagon secretion, 3-4 slowed gastric emptying, and enhanced splanchnic glucose uptake (resulting in a slowed appearance of meal-derived glucose into the circulation) (Kolterman et al, 2003; Cervera et al, 2008).

EQW (BYDUREON®) is an extended-release formulation of exenatide designed to provide continuous therapeutic concentrations of exenatide and offer patients the option of a weekly dosing regimen. It is approved by the US FDA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, (BYDUREON, 2014) and in the European Union as an adjunct to metformin, a sulfonylurea (SU), a thiazolidinedione (TZD), a combination of metformin and SU, or a combination of metformin and TZD, to improve glycemic control in adults with T2DM. Exenatide controls blood glucose by glucose dependently stimulating insulin secretion, suppressing glucagon secretion, slowing gastric emptying, and reducing food intake. BYDUREON consists of exenatide-containing polymeric microspheres for reconstitution in an aqueous vehicle. The biodegradable microspheres provide a gradual release of exenatide over predictable periods of time. Once weekly dosing with BYDUREON results in sustained steady-state plasma exenatide concentrations in a range known to be therapeutically effective based on the exenatide clinical development program. BYDUREON has demonstrated robust glucose-lowering effects in the fasting, preprandial, and postprandial states, resulting in improvement in 24-hour glucose control in patients with T2DM (Drucker et al, 2008).

BYDUREON has been studied as monotherapy in patients with type 2 diabetes who are taking metformin, an SU, a TZD, a combination of metformin and an SU, or a combination of metformin and a TZD, and still have not achieved adequate glycemic control (AstraZeneca Pharmaceuticals LP, 2014). BYDUREON has not been studied in patients with concomitant insulin use, in pediatric patients, in patients with a history of pancreatitis, in patients with acute or chronic hepatic impairment, or in patients with severe gastrointestinal disease. In addition, BYDUREON should not be used in patients with severe renal impairment or end-stage liver disease (BYDUREON, 2014).

Exenatide administration is generally safe and well-tolerated. The potential and identified risks of exenatide treatment have been well characterized through the exenatide twice daily (BID) and EQW development programs and postmarketing data for exenatide BID (BYETTA, 2014). The most frequent adverse events observed with exenatide are gastrointestinal in nature (nausea, vomiting, and diarrhea). Exenatide once weekly shows improved tolerability, specifically reduced nausea and vomiting, compared with exenatide BID, which may be

explained in part by the gradual increase in exenatide exposure to target therapeutic steady-state concentrations observed with the exenatide-containing microspheres. Injection-site related adverse events occurred more frequently with exenatide once weekly therapy relative to exenatide BID and were typically mild, transient, and resolved without interruption of therapy. Regardless of formulation, the risk of hypoglycemia was low with exenatide treatment (mostly mild to moderate in intensity), although an increased risk was observed when exenatide was used in combination with a SU or long-acting insulin. There was no evidence of increased duration or intensity of adverse events with prolonged exposure to exenatide (i.e., exenatide once weekly) as compared with intermittent exposure to exenatide (i.e., exenatide BID). Additional potential risks of exenatide therapy include treatment-emergent pancreatitis, renal failure, thyroid neoplasms, and the development of anti-exenatide antibodies (BYDUREON, 2014;AstraZeneca Pharmaceuticals LP, 2014).

Abnormal postprandial blood glucose values is one of the first signs of deteriorating glucose homeostasis in type 2 diabetes and the contribution of postprandial glucose excursions to hyperglycemia and overall glucose control is thought to be most significant in patients with lower hemoglobin A1c (HbA1c) values (Monnier, 2007; Monnier, 2003). For this reason, modifications of PPG excursions may be important for reaching treatment goals in some patients (Woerle, 2007). Current treatment guidelines provide targets for PPG levels of 140 mg/dL (Ceriello, 2008; Rodbard, 2007) and 180 mg/dL (American Diabetes Association, 2014). Fasting plasma glucose is as important to the understanding of the pathophysiology of diabetes as PPG. The purpose of this study is to evaluate the change in the 24-hour glucose profile after 4 and 10 weeks of BYDUREON treatment in patients inadequately controlled with metformin XR monotherapy. Associated changes in postprandial glucose levels and fasting glucose will also be determined.

1.2 Rationale for study design, doses, and control groups

This study will directly compare the effects on 24-hour mean weighted glucose of EQW vs. placebo on a background of metformin XR in Weeks 4 and 10 of treatment, to demonstrate that EQW provides continuous glucose control over 24 hours as early as Week 4 of treatment. Additionally, this study will also asses how well EQW can maintain a similar degree of continuous glycemic control for an individual patient after EQW is at steady state (during the 10^{th} week subsequent to initiation of treatment).

1.3 Benefit/risk and ethical assessment

Many patients with T2DM who receive pharmacological treatment are not reaching glycemic control goals. Currently available treatments for type 2 diabetes, including injectable insulin therapy and oral medications, have significant side-effects such as hypoglycemia and weight gain. There is therefore a need for better treatments for hyperglycemia and type 2 diabetes. The clinical effectiveness of BYDUREON has been demonstrated in 6 head-to-head randomized controlled clinical trials (N = 3223) in which HbA1c reductions ranged from 1.3% to 1.9% in patient with baseline A1c values of 8.3% to 8.6%. Direct comparative trials showed that HbA1c reductions with BYDUREON were significantly greater than HbA1c reductions with BYETTA, sitagliptin, pioglitazonem, or insulin glargine, but did not meet non-inferiority criteria compared with liraglutide in T2DM patients on 1 or more other glucose-lowering therapies. Treatment response to BYDUREON appeared to be consistent in all patient subgroups studied, including patients of different ages, races, and durations of diabetes. Evaluation of the clinical safety and efficacy data accumulated so far indicate an acceptable risk/benefit profile for BYDUREON 2 mg dose to be used in this study.

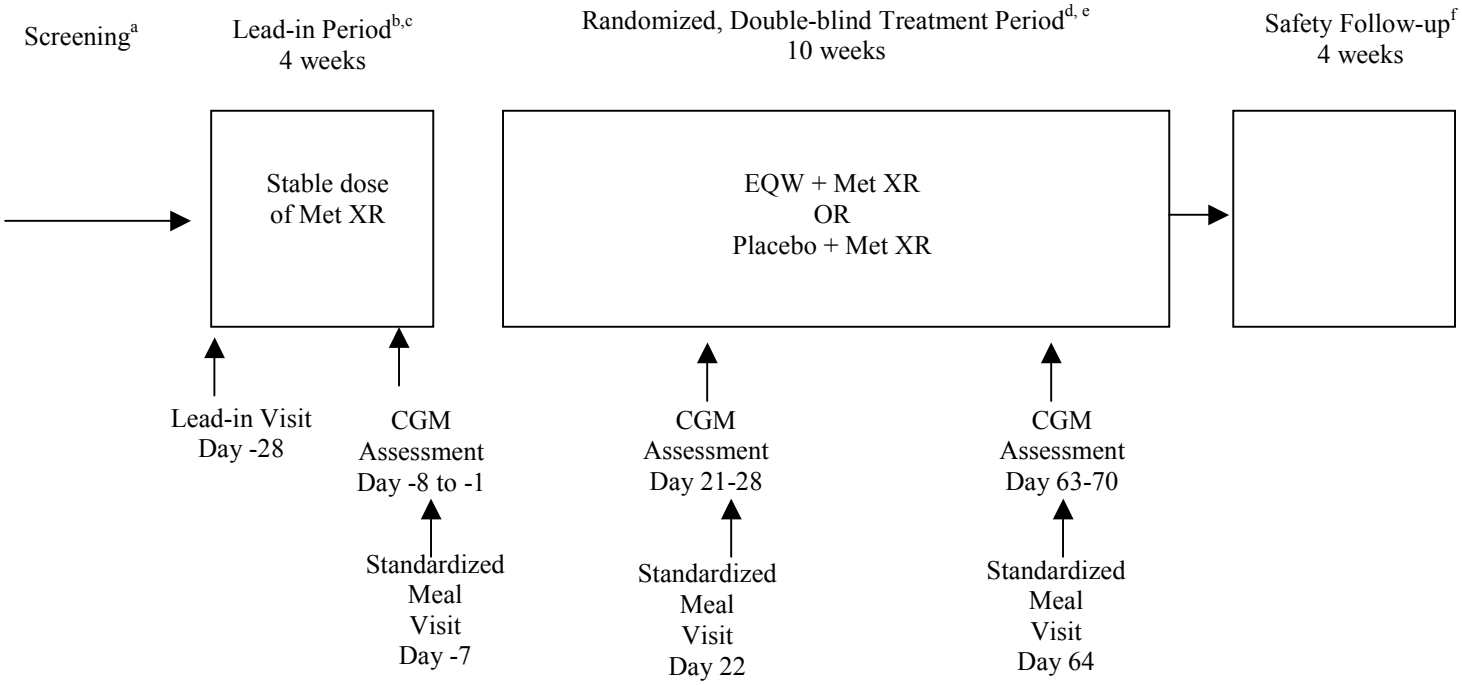
1.4 Study design

This will be a randomized, double-blind, parallel-group study comparing EQW vs. placebo in patients with T2DM treated with metformin XR. The patient population will consist of male and female patients ≥18 years and ≤75 years of age, inclusive, with T2DM who have inadequate glycemic control (HbA1c ≥7% and ≤10% at screening) who have been receiving a stable dose of metformin (≥1500 mg/day) for at least 8 weeks. Approximately 110 patients will be randomized in a 1:1 ratio (EQW:placebo) to achieve approximately 55 patients per treatment arm. After the 4-week lead-in period, patients will be randomized and then treated for 10 weeks. Following 10 weeks of treatment, standard safety assessments will be assessed during a 4-week follow-up period.

A continuous glucose monitoring (CGM) system will be used to measure the patient's interstitial glucose level. The 7 day assessment using the CGM will be performed during the lead-in period (Day -8 to Day -1), and during the Treatment Period (Day 21 to Day 28 and Day 63 to Day 70). The glucose measurements used for assessment of the primary endpoint will be analyzed from the CGM data.

A flow chart of the study design is provided in Figure 1.

Figure 1 Study flow chart



a) Patients with T2DM, on stable dose of metformin XR (≥1500 mg/day), and inadequate glucose control: HbA1c ≥7% and ≤10%.
b) Enter the single-blind medical nutrition and metformin XR lead-in phase.
c) Patients will undergo a 7-day CGM assessment during the lead in period (Day -8 to -1)
d) Patients will be randomized 1:1 to receive either EQW + open-label metformin XR (1500-2000 mg) OR placebo + open-label metformin XR (1500-2000 mg) once weekly.
e) Upon completion of the lead-in period, eligible patients will enter the 10-week, double-blind treatment period, followed by a 4-week follow-up period for safety assessments. All patients will undergo CGM blood glucose monitoring, for interstitial glucose from Day 21 to Day 28 and from Day 63 to Day 70.
f) The safety assessments will be collected at a 4-week follow-up visit.

CGM = continuous glucose monitoring; EQW = exenatide once weekly; HbA1c = hemoglobin A1c; Met = metformin; T2DM = type 2 diabetes mellitus.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To compare the effect on 24-hour mean weighted glucose after 4 and 10 weeks of treatment of EQW plus metformin with placebo plus metformin, using data obtained by a CGM system	Change in 24-hour mean weighted glucose from baseline (Day -1/1) to Day 6 of Week 10 (Day 69/70) and to Day 6 of Week 4 (Day 27/28)

2.2 Secondary objectives

Secondary Objectives:	**Outcome Measures:**
To examine the intra-patient variability of the change in 24-hour mean weighted glucose at the beginning and the end of the dosing cycle (Week 10 of treatment in EQW patients), using data obtained by a CGM system	Change in 24-hour mean weighted glucose between Day 1 of Week 10 (Day 64/65) and Day 6 of Week 10 (Day 69/70) within each EQW-treated patient
To compare the effect on fasting plasma glucose (FPG) and 2-hour PPG after 4 and 10 weeks of dosing of EQW plus metformin with placebo plus metformin	Change from baseline (Day 1) to Day 6 of Week 10 (Day 70) and Day 6 of Week 4 (Day 28) in FPG Change from baseline (Day -1) to Day 6 of Week 10 (Day 69) and Day 6 of Week 4 (Day 27) in 2-hour mean weighted PPG (after the breakfast meal)
To compare the following parameters after 4 and 10 weeks of dosing between the EQW plus metformin and placebo plus metformin treatment groups, using data obtained by a CGM system: the effect on 24-hour mean amplitude of glucose excursion (MAGE) the proportion of time patients who had plasma glucose measurements of: <70 mg/dL ≥70 mg/dL and ≤180 mg/dL or >180 mg/dL	Average of change in 24-hour mean weighted glucose from baseline (Day -1/1) to Days 1 to 6 of Week 10 and Week 4 calculated. (standard deviation [SD], MAGE, “Distance travel”, “Energy”)
To compare the effect on HbA1c levels and 2-hour PPG after 4 and 10 weeks of dosing of EQW plus metformin with placebo plus metformin	Change from baseline (Day -1) to Day 6 of Week 10 (Day 69) and Day 6 of Week 4 (Day 27) in 2-hour mean weighted PPG (after the breakfast meal)

2.3 Safety objectives (Not applicable)

2.4 Exploratory objective

Exploratory Objective:	Outcome Measure:
The difference in daily 24-hour mean weighted glucose during Week 10, within and between treatment groups, will be assessed and described descriptively. In addition, qualitative similarities and differences in each treatment group in daily CGM profiles will be evaluated.	Exploratory statistical parameters like "Distance traveled", the arch length of this curve and the other measures of "Energy" will be calculated

3. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfill the following criteria:

1. Is willing and able to give written informed consent prior to any study specific procedures;

2. Has diagnosis of T2DM treated with a stable dose of metformin (≥1500 mg/day), as monotherapy for at least 8 weeks prior to Screening;

3. Has a body mass index (BMI) ≤45 kg/m^2;

4. Has an HbA1c ≥7% and ≤10% obtained at Screening;

5. Has a fasting C-peptide concentration ≥1.0 ng/mL at Screening;

6. Is male or female, ages 18 to 75 years, inclusive;

7. Women of childbearing potential (WOCBP), defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy), must agree to use 2 medically accepted, effective methods of birth control (e.g., hormonal contraceptive, barrier contraceptive with additional spermicide, or an intrauterine device) beginning >30 days prior to study drug administration and continuing for 3 months after the end of the study;

8. Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of investigational product;

9. Women must not be breastfeeding;

10. Males who are sexually active with WOCBP must be surgically sterile or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides) for the duration of the study (from the time they sign consent) and for 3 months after the last dose of study medication to prevent pregnancy in a partner;

11. Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile) and azoospermic men do not require contraception. For this study, menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle-stimulating hormone (FSH) level >40 mIU/mL. Women treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used:

    - 1 week minimum for vaginal hormonal products (rings, creams, gels),
    - 4 week minimum for transdermal products,
    - 8 week minimum for oral products,
    - Other parenteral products may require washout periods as long as 6 months;

12. Has demonstrated good compliance with metformin XR (≥80 and ≤120%) during the lead-in period; and

13. Has demonstrated good compliance with the CGM device during the lead-in period, per Investigator decision.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff, Medpace staff, and/or staff at the study site);

2. Previous enrollment in the present study;

3. History of taking anti-hyperglycemic therapy other than metformin or metformin XR during the 8 weeks prior to Screening;

4. History of taking any DPP-4 inhibitor or pramlintide (SYMLIN) during the 12 weeks prior to Screening or during the study;

5. History of potent, inhaled, or intrapulmonary (including ADVAIR®) steroids known to have a high rate of systemic absorption during the 3 months prior to Screening or during the study;

6. History of prescription or over-the-counter weight loss medications during the 3 months prior to Screening or during the study;

7. Prior exposure to exenatide (including BYETTA, BYDUREON, or exenatide suspension) or any GLP-1 receptor agonist during the 6 months prior to Screening;

8. Prior exposure to dapagliflozin (FORXIGA, FARXIGA) or any sodium-glucose co-transporter 2 (SGLT-2) inhibitor during the 8 weeks prior to Screening;

9. Prior exposure to TZD during the 12 weeks prior to Screening;

10. Symptoms of poorly controlled diabetes that would preclude participation in this placebo-controlled trial, including but not limited to marked polyuria and polydipsia with greater than 10% weight loss during the last 3 months prior to Screening or other signs and symptoms;

11. History of diabetic ketoacidosis or hyperosmolar nonketotic coma;

12. Insulin therapy within 1 year of Screening (with the exception of insulin therapy during a hospitalization or use in gestational diabetes);

13. Significant cardiovascular history defined as:

    – History of myocardial infarction, coronary angioplasty or bypass graft(s), valvular disease or repair, unstable angina pectoris, transient ischemic attack, or cerebrovascular accidents within 6 months prior to study entry. Congestive heart failure defined as New York Heart Association stage III and IV and/or known left ventricular ejection fraction of ≤40%;

14. Repeated intermittent oral or inhaled corticosteroid treatment for periods lasting longer than 7 consecutive days during the 8 weeks prior to Screening. Patients receiving stable doses of replacement corticosteroid therapy for the 4 weeks prior to Screening may be enrolled;

15. Repeated intermittent thyroid replacement treatment (patients receiving stable doses of thyroid replacement for a minimum of 2 months prior to Screening may be enrolled);

16. Repeated intermittent anti-hypertensive agent treatment (patients receiving stable doses of anti-hypertensive for a minimum of 2 months prior to Screening may be enrolled);

17. Repeated intermittent anti-depressant treatment (patients receiving stable doses of antidepressants for a minimum of 2 months prior to Screening may be enrolled);

18. History of unstable or rapidly progressing renal disease, or severe renal impairment (creatinine clearance <30 mL/min);

19. History of alcohol or drug abuse within the previous 1 year;

20. Unstable major psychiatric disorders, as determined per the Investigator's discretion;

21. Immunocompromised individuals such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency virus;

22. History of hemoglobinopathies (sickle cell anemia or thalassemias, sideroblastic anemia);

23. Donation of blood or plasma to a blood bank within 3 months of Screening;

24. Administration of any other investigational drug or participation in a clinical research trial within 30 days of planned enrollment to this study;

25. History of acute pancreatitis associated or not with using an anti-diabetic drug therapy;

26. Has severe gastrointestinal disease, including gastroparesis;

27. Has acute or chronic hepatic impairment;

28. Has any condition which in the Investigator's opinion may render the patient unable to complete the study or which may pose significant risk to the patient;

29. Active liver disease and/or significant abnormal liver function defined as aspartate aminotransferase (AST) >3 × upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >3 × ULN and/or serum total bilirubin >2.0 mg/dL;

30. History of positive serologic evidence of current infectious liver disease including anti-HAV (IgM), HbsAg, or anti-HCV. Subjects who may have isolated positive anti-HBs may be included;

31. Personal history or family history of medullary thyroid carcinoma or inpatients with multiple endocrine neoplasia syndrome;

32. Serum creatinine (Scr) ≥1.5 mg/dL (132.6 µmol/L) for males and ≥1.4 mg/dL (123.8 µmol/L) for females;

33. Creatine kinase ≥3 × ULN;

34. Anemia of any etiology, defined as hemoglobin ≤12.0 g/dL (120 g/L) for men and hemoglobin ≤11.0 g/dL (110 g/L) for women;

35. Has an abnormal free T4 (Note: patients with an abnormal thyroid-stimulating hormone (TSH) value at Screening will be further evaluated by free T4);

36. Has any contraindication to therapy as outlined in the BYDUREON or metformin XR/metformin package inserts;

37. WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study and for up to 3 months after the last dose of investigational product;

38. WOCBP using a prohibited contraceptive method;

39. Women who are pregnant or breastfeeding;

40. Women with a positive pregnancy test on enrollment or prior to investigational product administration;

41. Prisoners or patients who are involuntarily incarcerated; or

42. Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

For procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrollment and randomization

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Determine patient eligibility. See Section 3.

3. If a patient withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

At Screening, the site will assign each patient a unique sequential patient number and enter this number into the interactive voice response system/interactive web response system (IVRS/IWRS). The patient number will consist of the letter E and a 7 digit number (the 4 digit site number and 3 digit patient number). This number will be used for identification throughout the study and will not be used for any other participant.

Patients entering the lead-in period

At the time of entry into the lead-in period, the patients will receive a pharmacy card to obtain their metformin XR.

Patients entering the double-blind treatment period

Following completion of the lead-in period, patients eligible for double-blind treatment will be randomly assigned to 1 of the 2 treatment arms by the IVRS/IWRS in a 1:1 ratio using a blocked randomization schedule:

- EQW (BYDUREON [exenatide extended-release for injectable suspension]) + metformin XR
- Placebo injection similar to EQW + metformin XR

The treatment assignment will be balanced within each site by the IVRS/IWRS through block allocation to sites. Randomization schedules will be generated and kept by AstraZeneca. At all study visits when study medication is dispensed, each patient will be assigned a kit number by the IVRS/IWRS. Kit numbers will be recorded on the eCRF. The IVRS/IWRS will be available 24 hours per day, 7 days a week.

If a dose is missed, it should be administered as soon as noticed, provided the next regularly scheduled dose is due at least 3 days later. If the next regularly scheduled dose is due within less than 3 days, then the missed dose should be skipped. Thereafter, patients can resume their usual dosing schedule of once every 7 days (weekly).

3.6 Methods for ensuring blinding

This is a double-blind study. Patients, investigators, and study personnel will remain blinded throughout the study. The AstraZeneca US Medical Lead & External Statistician will have access to unblinded data. IVRS/IWRS will be used to manage randomization to treatment arms in a blinded manner. To ensure blinding of treatments, the placebo injection will be packaged to match the single-dose trays used for investigational product (IP) during the treatment period.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

3.8 Restrictions

Patients are not permitted to use acetaminophen or paracetamol during the study, as these drugs may interfere with the CGM device.

Patients are to continue metformin XR during the study. Patients should discontinue other oral anti-hyperglycemic medications at least 4 weeks prior to Screening. The intent of this study is that patients do not deviate from their metformin regimen. However, in circumstances where a patient has a fasting glucose value above 270 mg/dL for 3 consecutive visits then the dose of metformin XR may be increased to the maximum dose of 2000 mg. This dose may be continued for the duration of the study. If such a situation occurs that patients are still not under 270 mg/dL fasting glucose after this increase in metformin XR dose then a decision to keep the patient in the study should be made only after consultation between the Investigator and the AstraZeneca clinical research physician. The decision should be documented by a note to the Investigator’s file.

3.8.1 Dietary guidance/restrictions

Beginning in the lead-in period, and continuing throughout the study, patients will be asked to follow instructions on medical nutrition in accordance with the American Diabetes Association (ADA) dietary guidelines or locally accepted guidelines. Patients will be provided with instructional material and training regarding the medical nutrition guidelines. Patients will be asked to follow a standard diabetic weight maintaining diet containing approximately 55% carbohydrate, 25% fat, and 20% protein. The total daily caloric intake for each patient will be limited to approximately 2000 kcal.

The timing and content of meals should remain consistent across the 7-day CGM system monitoring period. The timing and content of meals should be similar from the 7-day CGM testing at baseline vs. CGM testing during the treatment period to ensure comparability of data.

In order to keep the timing and content of meals consistent patients should avoid significant changes during 7-day CGM assessments (i.e., typical portion sizes, same pattern/meals when dining at restaurants, avoiding holidays/celebratory meals, etc).

Patients will be provided a standardized breakfast meal following guidelines at the study site on Day -7, Day 22, and Day 64. The standardized breakfast meal should account for approximately 35% of the daily calorie intake (~700 kcal). After the meal is given, only water will be provided through the completion of the meal test.

3.9 Discontinuation of investigational product

Patients MUST discontinue investigational product (and non-investigational product at the discretion of the Investigator) for any of the following reasons:

- Patient's request to stop study treatment;
- Any clinical adverse event, laboratory abnormality, or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the patient;
- Pregnancy;
- Termination of the study by AstraZeneca;
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness; or
- Unblinding a patient for any reason (emergency or non-emergency).

3.9.1 Discontinuation due to hyperglycemia (pre-specified glycemic parameters)

Discontinuation due to hyperglycemia during treatment

Patients will be instructed to perform fasting self-blood glucose monitoring (SBGM) during the study. Patients who have a fasting fingerstick glucose of ≥270 mg/dL (15 mmol/L) on 3 consecutive days will be instructed to call the Investigator site. The patient will be scheduled for a FPG performed by the central laboratory. If the FPG by central laboratory is ≥270 mg/dL or 15 mmol/L, the patient will be discontinued. If at the Day -7 visit, the patient has not been consistently performing fasting SBGM and his or her central laboratory FPG ≥270 mg/dL, the patient will be considered for discontinuation.

Table 1 Discontinuation criteria for patients who experience hyperglycemia during treatment

Discontinuation criteria by FPG during treatment	
At a site visit	**FPG mg/dL (mmol/L)**
Fingerstick (FPG)	≥270 mg/dL (15.0 mmol/L) for 3 consecutive days
Central laboratory (FPG)	≥270 (15.0 mmol/L), if has not performed FPG

3.9.1.1 Discontinuation due to hypoglycemia or symptoms suggestive of hypoglycemia

Blinded study medication or open-label metformin XR should not be down-titrated and patients should not be discontinued from any treatment phase based on single episodes of hypoglycemia or symptoms of hypoglycemia unless clinically indicated. The assessment of a single fingerstick or central laboratory glucose value should not be the sole assessment used to determine patient discontinuation due to hypoglycemia. Clinical indications for discontinuation due to hypoglycemia may include the following:

- Symptoms suggestive of hypoglycemia (e.g., sweating, shakiness, increased heart rate, confusion, dizziness, lightheadedness, or hunger) in the absence of environmental factors known to contribute to hypoglycemia (i.e., excess physical activity, concurrent illness, or missed or delayed meal) and/or

- Documented fingerstick plasma glucose values ≤50 mg/dL (2.8 mmol/L) on multiple occasions (2 or more occasions).

A patient may also be discontinued from the study due to severe hypoglycemia as determined by the Investigator. **No down-titration of blinded study medication or metformin XR will be allowed at any time during the study except in cases noted in Section 7.7.**

If fingerstick glucose values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the patient's glucose meter should be tested and the procedure for using it reviewed with the patient.

3.9.1.2 Discontinuation due to elevated serum creatinine

During the lead-in period, patients with a Scr ≥1.5 mg/dL (132.6 µmol/L) in males or ≥1.4 mg/dL (123.8 µmol/L) in females will be discontinued from the study.

- During the double-blind treatment period, patients with a Scr ≥1.5 mg/dL (132.6 µmol/L) but <2.0 mg/dL (176 µmol/L) in males or ≥1.4 mg/dL (123.8 µmol/L) but <2.0 mg/dL (176 µmol/L) in females, will have their open-label metformin XR held and a confirmatory repeat Scr drawn within 1 week. If the repeat Scr is ≥1.5 mg/dL (132.6 µmol/L) in males or ≥1.4 mg/dL (123.8 µmol/L) in females, the patient must be immediately discontinued from the study, AstraZeneca notified, and an early discontinuation visit performed which will include samples for the assessment of plasma concentrations. If the repeat Scr is <1.5 mg/dL (males) or <1.4 mg/dL (females), study medication may be resumed unless otherwise contraindicated.

- During the double-blind treatment period, patients (males and females) with a Scr ≥2.0 mg/dL (176 µmol/L), will have both blinded study medication and open-label metformin XR held and a confirmatory repeat Scr drawn within 1 week. If the repeat Scr is ≥1.5 mg/dL (132.6 µmol/L) in males or ≥1.4 mg/dL (123.8 µmol/L) in females, the patient must be immediately discontinued from the study, AstraZeneca notified, and an early discontinuation visit performed which will include samples for plasma concentrations. If the repeat Scr is <1.5 mg/dL (males) or <1.4 mg/dL (females), study medication may be resumed unless otherwise contraindicated.

3.9.2 Discontinuation due to elevated liver enzymes

The Investigator and the AstraZeneca representative will be notified by the central laboratory when any patient experiences elevation of liver enzymes AST >3 × ULN (40 U/L for men and 72 U/L for women) and/or ALT >3 × ULN (80 U/L for men and 72 U/L for women) and/or serum total bilirubin >2.0 mg/dL. The study medication should be discontinued immediately and a repeat blood sample should be taken. Appropriate follow-up should be arranged for the patient.

3.9.3 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 3.10), without prejudice to further treatment. A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (see Section 6); and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 3.10.

3.9.4 Lost to follow-up

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by patient to 1 registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death.

If the Investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the Investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the patient's medical records.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrollment' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events. The Investigator will follow up adverse events outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant

- FPG level ≥270 mg/dL (see Table 1)
- Are assessed as causally related to study drug
- Are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 2 Study plan

	Screening[a]	Lead-in Period[a]				Randomization and Double-blind Treatment Period									ET[b]	Follow-up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Week	**-4**		**-2**	**-1**		**1**	**2**	**3**	**4**		**9**		**10**			
Day		**-28**	**-8**	**-7[c]**	**-1**	**1**	**15**	**21**	**22[c]**	**28**	**57**	**63**	**64[c]**	**70**		
Written informed consent	X															
Inclusion/exclusion criteria	X					X										
Medical/surgical history	X															
Physical examination	X[d]	X		X[d]		X[d]	X[d]		X		X[d]		X	X[d]	X	X[d]
Vital signs	X	X		X	X	X	X		X		X		X	X	X	X
Body weight	X	X		X	X	X	X		X		X		X	X	X	X
Height	X															
BMI	X															
12-lead ECG		X							X				X	X	X	
Review concomitant medication	X	X		X	X	X	X		X				X	X	X	X
Medical nutrition instruction/review		X		X	X	X	X		X	X	X		X			

	Screening[a]	Lead-in Period[a]				Randomization and Double-blind Treatment Period									ET[b]	Follow-up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Week	**-4**		**-2**	**-1**		**1**	**2**	**3**	**4**		**9**		**10**			
Day		**-28**	**-8**	**-7[c]**	**-1**	**1**	**15**	**21**	**22[c]**	**28**	**57**	**63**	**64[c]**	**70**		
Dispense glucose meter and supplies/provide instruction		X	X			X	X	X			X	X				
Adverse event review (AEs and SAEs)		X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Samples for standard laboratory panel[f]	X			X		X	X		X		X		X	X	X[e]	X
Urine pregnancy test[g]	X					X							X		X	
Calcitonin sample				X												
HbA1c	X					X	X		X		X		X	X	X	
FPG	X			X		X	X		X		X		X	X	X	
Postprandial glucose test/standardized meal[h]				X					X				X			
PK blood sampling						X	X		X		X		X	X	X	
Biomarker blood sampling						X	X		X		X		X	X	X	

	Screening[a]	Lead-in Period[a]				Randomization and Double-blind Treatment Period										
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**ET[b]**	**Follow-up**
Week	**-4**		**-2**	**-1**		**1**	**2**	**3**	**4**		**9**		**10**			
Day		**-28**	**-8**	**-7[c]**	**-1**	**1**	**15**	**21**	**22[c]**	**28**	**57**	**63**	**64[c]**	**70**		
Assess glycemic discontinuation criteria	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH	X[i]															
Hepatic screening panel[j]	X															
Insert CGM system			X[l]					X[l]				X[l]				
Remove CGM system					X[l]					X[l]				X[l]	X[l]	
Self-blood glucose monitoring/ CGM calibration[k]			X[l]		X[l]			X[l]				X[l]				
Review compliance			X			X	X	X		X	X	X		X	X	
Treatment dispensed[m]		X[n]				X				X	X					

Note: Entry into the lead-in period (Day -28) should occur at least 7 days after Screening but no later than 14 days after receiving the Screening laboratory results. Study visits during the lead-in period and the double-blind treatment period should occur on the designated visit day ± 3 days.

a. Screening can be performed over multiple visits. Entry into the lead-in period should occur at least 7 days after Screening and no later than 14 days after screening.

b. If the patient discontinues during one of the 7 day CGM periods, remove CGM device. The CGM device should not remain in place longer than 10 days.

c. Standard safety blood tests, urinalysis for safety analysis, and HbA1c will be performed 30 minutes prior to the standardized breakfast meal.

d. A complete physical examination will be performed on days designated with an X. A brief physical examination will be performed on days designated with an X[d]. See Section 5.2.2 for details.

e. If patient is discontinuing the study due to an adverse event, a 5 mL blood sample for assessment of exenatide plasma concentration will be collected.

f. See Table 4 for a list of the safety laboratory variables for this study. Patients who discontinue should have a standard safety laboratory panel collected at the conclusion of their participation.

g. Women of childbearing potential only.

h. Glucose levels will be drawn 30 minutes before and just prior to breakfast and 30, 60, 120, and 180 minutes after breakfast. The post meal glucose tolerance test is provided in a 3 day window.

i. Patients must be fasting at this time point.

j. Includes hepatitis screen panel (anti-hepatitis C virus and HBsAg only).

k. Patients should be instructed to perform fasting SBGM daily, and instructed to call the site if they have a FPG ≥270 mg/dL (15 mmol/L) for 3 consecutive days. The patient should have a FPG by central laboratory; if ≥270 mg/dL (15 mmol/L), the patient should be discontinued. If the patient has not performed fasting SBGM and the central laboratory FPG at Day -7 ≥270 mg/dL (15 mmol/L), the patient should be considered for discontinuation.

l. Review instructions for sampling SBGM. (Refer to Section 5.2.6.1). The CGM sensor will be inserted on Day -8, Day 21, and Day 63 at evening time with the calibrating on site. If patients are not tracking to have the required number of measures, they will need to be rescheduled. Patients will be instructed to calibrate the CGM system device according to manufacturer's instructions every 12 hours.

m. During the lead-in period, patients will be instructed to take 3-4 tablets of open-label metformin XR with the evening meal (1500-2000 mg). During the double-blind treatment period, patients will be instructed to take either EQW + open-label metformin XR (1500-2000 mg) OR placebo + open-label metformin XR (1500-2000 mg) once weekly (Day 7 each week). The double-blind study medication (either EQW or placebo) will be administered subcutaneously once weekly and the metformin XR will be taken once daily with the evening meal.

n. First dose of metformin XR to be taken in the evening. Instruct patient to write down the time of first dose. Patient should be contacted the following day to obtain date and time of first dose.

AE = adverse event; BMI = body mass index; CGM = continuous glucose monitoring; ECG = electrocardiogram; ET = early termination; EQW = exenatide extended release once weekly; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; PK = pharmacokinetic; SAE = serious adverse event; SBGM = self-blood glucose monitoring.

Table 3 Procedures before and after the standard meal (Day -7, Day 22, and Day 64)

Assessment	Minutes after the start of the standard meal						
	-60	**-30**	**0**	**30**	**60**	**120**	**180**
Standardized meal[a]			X				
Confirm CGM system	X						
PK blood sampling[b]			X				
Biomarker blood sampling[b]			X				
Glucose		X	X[b]	X	X	X	X
Insulin			X[b]	X	X	X	X
Glucagon			X[b]				
C-peptide			X[b]	X	X	X	X
Safety assessments[c]		X					

Note: PPGT test will be provided in a 3 day window around the day marked in the schedule. There is a window of ±2 minutes for sampling time points.

a. Note the time the meal was started and completed and record on the CRF. The patient should consume the entire meal within 30 minutes. The time of commencement of the breakfast meal on the day of the visit will be considered the 0 time point for all testing. The meals and timing of meals at the Day -7 must be replicated at the Day 22 and Day 64 visits.
b. Collect sample prior to the breakfast meal (at -5 minutes). Note: PK and Biomarker samples will only be taken on Day 22 and Day 64.
c. Collect blood and urine sample for standard safety laboratory assessments. See Table 4. Standard safety blood tests, urinalysis for safety analysis, and HbA1c will be performed 30 minutes prior to the standardized meal.

CGM = continuous glucose monitoring; eCRF = electronic case report form; HbA1c = hemoglobin A1c; PK = pharmacokinetic; PPGT = postprandial glucose tolerance.

4.1 Enrollment/screening period

4.1.1 Screening (Visit 1)

Patients will be screened for study participation and eligibility will be determined by assessment of inclusion and exclusion criteria listed in Sections 3.1 and 3.2. Patients who do not meet the eligibility criteria must not be enrolled in the study. All patients will provide written informed consent prior to any study procedure or change in medical therapy required by protocol. Study procedures will be performed as listed in Table 2.

Samples will be taken from patients for FPG, HbA1c, and safety laboratory assessments. See Table 4 for a list of the safety laboratory variables.

At this visit, the site will assign each patient a unique sequential patient number and enter this number into the IVRS/IWRS.

Prior to the end of this visit, the patient should be scheduled for the Lead-in Visit (Day -28) and informed that fasting is not required.

Commencement into the medical nutrition and metformin XR lead-in period should begin at least 7 days after, but within 14 days of receiving the screening visit laboratory results.

4.1.2 Lead-in period (Visit 2 to Visit 5)

The medical nutrition and metformin XR lead-in period will be 28 days.

If all inclusion criteria have been met without the presence of any exclusion criteria, the patient may be started on the lead-in period study medication.

During the lead-in period, patients will be instructed to take 3-4 tablets of open-label metformin XR once daily with the evening meal (1500-2000 mg). If a patient is on 1500 mg of metformin XR at screening, they will receive 1500 mg metformin XR during the lead-in period. If a patient is on 2000 mg of metformin XR at screening, they will receive 2000 mg metformin XR during the lead-in period. Patients on 2500 mg or 2550 mg of metformin XR daily (850 mg three times a day) will receive 2000 mg of metformin XR.

Patients will be counseled on medical nutrition by a qualified member of the study staff beginning with the first lead-in visit. At the lead-in visit, the patient's current dietary and exercise behavior will be reviewed. Patients will be instructed on medical nutrition in accordance with the ADA guidelines or locally accepted guidelines. Home glucose meters and supplies will be dispensed to patients and SBGM requirements and procedures will be explained (see Section 5.2.6.1). Daily SBGM will be performed throughout the lead-in period. The medical nutrition plan will be reinforced at visits on Day -28, -7, -1, 1, 15, 22, 28, 57, and 64. Patients will be asked to keep a food diary and to record both meal times and portion size. Patients will be asked to bring the food diary in for review during site visits and will return home with the diary.

The lead-in CGM data will be reviewed for compliance. During the 7-day CGM period required during the lead-in phase of the study a 70% compliance rate is required in order to ensure the patient will be randomized.

4.1.2.1 Lead-In Visit, Day -28, Visit 2

Patients are to arrive at their study visit on Day -28. Study procedures will be performed as listed in Table 2. Patients will be provide with a pharmacy card to receive their metformin XR at this visit.

Patients will be instructed to take 3-4 tablets of open-label metformin XR once daily with the evening meal (1500-2000 mg).

In addition, patients will be reminded:

- To call the investigative site if the fasting daily glucose on 3 consecutive days is ≥270 mg/dL (15 mmol/L).
- To bring study medication and glucose meter to the next scheduled study visit.
- That the insertion and calibration of the CGM system device will take approximately 2 hours at the next study visit and the patient must re-calibrate the CGM system device every 12 hours per manufacturer's instructions.
- To abstain from tobacco, alcohol, and caffeine for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.
- Nicotine or nicotine replacement therapy may not be used for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.
- To refrain from strenuous exercise, contact sports, and sunbathing for the 24 hours prior to all study site visits.

Prior to the end of this visit, the patient will be scheduled for the next study visit (Day -8), to occur prior to 16:00.

4.1.2.2 Lead-In Visit, Day -8, Visit 3

The primary purpose of the Day -8 visit is to place the CGM device, calibrate it, and provide training to the patient on its use in preparation for the standardized breakfast meal visit on Day -7 and the subsequent 7-day CGM assessment. Patients are to arrive at their study visit prior to 16:00. Study procedures will be performed as listed in Table 2. The IVRS/IWRS should be notified if the patient is discontinued from the study. The patient will obtain his or her fingerstick blood glucose level and input it to the CGM sensor as calibration points.

The CGM system sensor will be inserted, and confirmation that the system is working properly will be obtained. Patients will be sent home with instructions regarding calibration

2 hours after insertion, post dinner, before bedtime, and a fasting assessment the next morning, then calibrate every 12 hours (see Section 5.2.6.2). Patients should be reminded that the timing and content of meals should remain consistent across the 7-day CGM system monitoring period. See Section 3.8.1 for details on the meals. The SBGM measurements/records, and the calibration and function of the CGM system device should be reviewed.

Patients will be instructed to take 3-4 tablets of open-label metformin XR once daily with the evening meal (1500-2000 mg).

Patients should be reminded about fasting requirements (at least 8 hours) prior to the Day -7 visit.

In addition, patients should be reminded:

- To bring study medication and glucose meter to the next scheduled study visit.
- To abstain from tobacco, alcohol, and caffeine for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.
- Nicotine or nicotine replacement therapy may not be used for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.
- To refrain from strenuous exercise, contact sports, and sunbathing for the 24 hours prior to all study site visits.
- To call the investigative site if the fasting daily glucose on 3 consecutive days is ≥270 mg/dL (15 mmol/L).
- The patient must re-calibrate the CGM system device every 12 hours per manufacturer's instructions.

Prior to the end of this visit, the patient will be scheduled to return on Day -7 (with a 3 day window as Day -7, -6, and -5) for the standardized breakfast meal PPG tolerance (PPGT) test, to occur between 06:00-10:00.

4.1.2.3 Lead-in Visit, Day -7 (Day -7; -6; -5 window), Visit 4

Day -7 is a standardized breakfast meal PPGT test visit. Patients are to arrive at their study visit between 06:00-10:00. Study procedures will be performed as listed in Table 2. The IVRS/IWRS should be notified if the patient is discontinued from the study.

Samples will be taken from patients for calcitonin, FPG, HbA1c, and safety laboratory assessments. See Table 4 for a list of the safety laboratory variables.

Patients will be provided a standardized breakfast following guidelines at the study site. The standardized breakfast meal should account for approximately 35% of the daily calorie intake (~700 kcal). The meal should be consumed in 30 minutes. These meals will remain consistent across the Day -7, Day 22, and Day 64 visits. For details on the procedures before and after the breakfast meal, see Section 5.3.1.

Patients should be reminded that the timing and content of meals should remain consistent across the 7-day CGM system monitoring period. See Section 3.8.1 for details on the meals. Self-blood glucose monitoring measurements/records and the calibration and function of the CGM system device should be reviewed.

The calibration of the CGM system device will take approximately 2 hours and the patient must re-calibrate the CGM system device every 12 hours per manufacturer's instructions.

Patients will be instructed to take 3-4 tablets of open-label metformin XR once daily with the evening meal (1500-2000 mg).

Prior to leaving the study site at this visit, patients will be scheduled to return to the site prior to 16:00 on Day -1. The day of CGM sensor removing is mandatory on Day -1 of the study. The last day of the lead-in period (Day -1) and the pre-randomization visit will be the same day for patients who qualify for, and are to be randomized into, the double-blind treatment period.

4.1.2.4 Lead-in Visit, Day -1, Visit 5

The purpose of the Day -1 Visit is to remove the CGM device (the CGM device should not remain in place longer than 10 days). Patients are to arrive at their study visit prior to 16:00. Study procedures will be performed as listed in Table 2. The IVRS/IWRS should be notified if the patient is discontinued from the study.

The patient will obtain his or her fingerstick blood glucose level and input it to the CGM sensor as calibration points.

Patients will be instructed to take 3-4 tablets of open-label metformin XR once daily with the evening meal (1500-2000 mg).

In addition, patients should be reminded:

- Of the fasting requirements for the Day 1 visit (no food or drink except water at least 8 hours prior to visit).
- To call the investigative site if the fasting daily glucose on 3 consecutive days is ≥270 mg/dL (15 mmol/L).
- To bring lead-in study medication and glucose meter to the next scheduled study visit.

- To abstain from tobacco, nicotine or nicotine replacement, alcohol, and caffeine for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.

- To refrain from strenuous exercise, contact sports, and sunbathing for the 24 hours prior to all study site visits.

Prior to leaving the study site at this visit, patients will be scheduled to return to the site on Day 1.

4.2 Treatment period

During the double-blind treatment period, patients will be instructed to take either EQW + open-label metformin XR (1500-2000 mg) OR placebo + open-label metformin XR (1500-2000 mg) once weekly (Day 7 each week). Patients will continue to take metformin XR once daily with the evening meal.

4.2.1 Randomization, Day 1, Visit 6

Patients are to arrive at their study visit on Day 1. Study procedures will be performed as listed in Table 2. The IVRS/IWRS should be notified if the patient is discontinued from the study.

The patient's eligibility for randomization will be confirmed (see Inclusion criteria Section 3.1 and Exclusion criteria Section 3.2). The data from the CGM device from the 7-day CGM period during the lead-in will be reviewed for compliance. A 70% compliance rate is required to randomize the patient.

Samples will be taken from patients for FPG, HbA1c, and safety laboratory assessments. See Table 4 for a list of the safety laboratory variables.

At the conclusion of the Day 1 visit, the patient will be randomized via IVRS/IWRS, and the double-blind study drugs (EQW or placebo) will be assigned and dispensed.

Patients will take their first dose of double-blind study medication at the site. The time of first dose will be noted on the eCRF. Patients will be trained on IP administration at this visit.

Patients will take their open-label metformin XR with the evening meal.

Patients will remain at the study site for collection of pharmacokinetic (PK) and biomarker blood samples according to the sampling described below:

- Perform PK blood sampling (see Section 5.4).

- Collect blood samples for biomarker analysis (see Section 5.7).

Prior to leaving the study site at the end of visit on Day 1, the patient will be scheduled for a Day 15 visit.

In addition, patients will be reminded:

- Of the fasting requirements for the Day 15 visit (at least 8 hours prior to visit).
- To call the investigative site if the fasting daily glucose on 3 consecutive days is ≥270 mg/dL (15 mmol/L).
- To bring study medication and glucose meter to the next scheduled study visit.
- To abstain from tobacco, nicotine or nicotine replacement, alcohol, and caffeine for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.
- To refrain from strenuous exercise, contact sports, and sunbathing for the 24 hours prior to all study site visits.
- To take the double-blind study medication once weekly (Day 7 each week). Patients will continue to take metformin XR once daily with the evening meal.

4.2.2 Day 15, Visit 7

Patients are to arrive at their study visit on Day 15. Study procedures will be performed as listed in Table 2.

The IVRS/IWRS should be notified if the patient is discontinued from the study. Patients will remain at the study site for collection of PK and biomarker blood samples according the sampling described below:

- Perform PK blood sampling (see Section 5.4).
- Collect blood samples for biomarker analysis (see Section 5.7).

Additionally, samples will be taken from patients for FPG, HbA1c, and safety laboratory assessments. See Table 4 for a list of the safety laboratory variables.

Patients will take their dose of double-blind study medication with time of dose noted on the eCRF if the patient is due for their weekly dose of double-blind study medication.

Prior to leaving the study site at the end of visit on Day 15, the patient will be scheduled for a Day 21 visit, occurring prior to 16:00.

In addition, patients will be reminded:

- To call the investigative site if the fasting daily glucose on 3 consecutive days is ≥270 mg/dL (15 mmol/L).
- That the insertion and calibration of the CGM system device will take approximately 2 hours at the next study visit and the patient must re-calibrate the CGM system device every 12 hours per manufacturer's instructions.
- To bring study medication and glucose meter to the next scheduled study visit.
- To abstain from tobacco, nicotine or nicotine replacement, alcohol, and caffeine for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.
- To refrain from strenuous exercise, contact sports, and sunbathing for the 24 hours prior to all study site visits.
- To take the double-blind study medication once weekly (Day 7 each week). Patients will continue to take metformin XR once daily with the evening meal.

4.2.3 Day 21, Visit 8

Patients are to arrive at their study visit prior to 16:00. Study procedures will be performed as listed in Table 2. The IVRS/IWRS should be notified if the patient is discontinued from the study. The patient will obtain his or her fingerstick blood glucose level and input it to the CGM sensor as calibration points.

The CGM system sensor will be inserted, and confirmation that the system is working properly will be obtained. Patients will be sent home with instructions regarding calibration (every 12 hours, see Section 5.2.6.2).

Patients will take their open-label metformin XR and their dose of double-blind study medication with time of dose noted on the eCRF if the patient is due for their weekly dose of double-blind study medication.

In addition, patients should be reminded:

- Of the fasting requirements for the Day 22 visit (at least 8 hours prior to visit).
- To bring study medication and glucose meter to the next scheduled study visit.
- To call the investigative site if the fasting daily glucose on 3 consecutive days is ≥270 mg/dL (15 mmol/L).
- That the patient must re-calibrate the CGM system device every 12 hours per manufacturer's instructions.

- To bring study medication and glucose meter to the next scheduled study visit and not to administer metformin XR on the morning of the visit.

- To abstain from tobacco, nicotine or nicotine replacement, alcohol, and caffeine for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.

- The timing and content of meals should remain consistent across the 7-day CGM system monitoring period. See Section 3.8.1 for details.

- To refrain from strenuous exercise, contact sports, and sunbathing for the 24 hours prior to the study site visit

- To take the double-blind study medication once weekly (Day 7 each week). Patients will continue to take metformin XR once daily with the evening meal.

Prior to the end of this visit, the patient will be scheduled to return on Day 22 (Week 4), for the standardized breakfast meal PPGT test, to occur between 06:00-10:00.

4.2.4 Day 22, (Day 22, 23, 24 window), Visit 9

Patients are to arrive at their study visit on Day 22 between 06:00-10:00. Study procedures will be performed as listed in Table 2.

The IVRS/IWRS should be notified if the patient is discontinued from the study. Patients will remain at the study site for collection of PK and biomarker blood samples according the sampling described below:

- Perform PK blood sampling prior to the meal (see Section 5.4).

- Collect blood samples for biomarker analysis prior to the meal (see Section 5.7).

Additionally, samples will be taken from patients for FPG, HbA1c, and safety laboratory assessments. See Table 4 for a list of the safety laboratory variables.

Patients will be provided a standardized breakfast following guidelines at the study site. The standardized breakfast meal should account for approximately 35% of the daily calorie intake (~700 kcal). The meal should be consumed in 30 minutes. These meals will remain consistent across the Day -7, 22, and Day 64 visits.

For details on the procedures before and after the breakfast meal, see Section 5.3.1.

Patients will administer their dose of double-blind study medication with time of dose noted on the eCRF if the patient is due for their weekly dose of double-blind study medication.

In addition, patients will be reminded:

- To call the investigative site if the fasting daily glucose on 3 consecutive days is ≥270 mg/dL (15 mmol/L).
- That the patient must re-calibrate the CGM system device every 12 hours per manufacturer's instructions.
- To bring study medication and glucose meter to the next scheduled study visit.
- To abstain from tobacco, nicotine or nicotine replacement, alcohol, and caffeine for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.
- The timing and content of meals should remain consistent across the 7-day CGM system monitoring period. See Section 3.8.1 for details.
- To refrain from strenuous exercise, contact sports, and sunbathing for the 24 hours prior to all study site visits.
- To take their open-label metformin XR and their dose of double-blind study medication with time of dose noted on the eCRF if the patient is due for their weekly dose of double-blind study medication.

Prior to the end of this visit, the patient will be scheduled for the next study visit (Day 28 with 26, 27, 28 window), to occur prior to 18:00.

4.2.5 Day 28, Visit 10

Patients are to arrive at their study visit prior to 18:00 (Day 28, Week 4) for removing of the CGM sensor. Study procedures will be performed as listed in Table 2. The IVRS/IWRS should be notified if the patient is discontinued from the study.

Study medication will be dispensed. Patients will take their open-label metformin XR and their dose of double-blind study medication with time of dose noted on the eCRF if the patient is due for their weekly dose of double-blind study medication.

Prior to leaving the study site at the end of visit on Day 28, the patient will be scheduled for a Day 57 visit.

In addition, patients should be reminded:

- Of the fasting requirements for the Day 57 visit (at least 8 hours prior to visit).
- To call the investigative site if the fasting daily glucose on 3 consecutive days is ≥270 mg/dL (15 mmol/L).
- To bring study medication and glucose meter to the next scheduled study visit.

- To abstain from tobacco, nicotine or nicotine replacement, alcohol, and caffeine for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.

- To refrain from strenuous exercise, contact sports, and sunbathing for the 24 hours prior to all study site visits.

- To take their open-label metformin XR and their dose of double-blind study medication with time of dose noted on the eCRF if the patient is due for their weekly dose of double-blind study medication.

4.2.6 Day 57, Visit 11

Patients are to arrive at their study visit on Day 57. Study procedures will be performed as listed in Table 2.

The IVRS/IWRS should be notified if the patient is discontinued from the study. Patients will remain at the study site for collection of PK and biomarker blood samples according the sampling described below:

- Perform PK blood sampling (see Section 5.4).

- Collect blood samples for biomarker analysis (see Section 5.7).

Additionally, samples will be taken from patients for FPG, HbA1c, and safety laboratory assessments. See Table 4 for a list of the safety laboratory variables.

Study medication will be dispensed. Patients will take their dose of double-blind study medication with time of dose noted on the eCRF if the patient is due for their weekly dose of double-blind study medication.

Prior to the end of this visit, the patient will be scheduled for the next study visit (Day 63), to occur prior to 16:00.

In addition, patients will be reminded:

- To call the investigative site if the fasting daily glucose on 3 consecutive days is ≥270 mg/dL (15 mmol/L).

- That the insertion and calibration of the CGM system device will take approximately 2 hours at the next study visit and the patient must re-calibrate the CGM system device every 12 hours per manufacturer's instructions.

- To bring study medication and glucose meter to the next scheduled study visit.

- To abstain from tobacco, nicotine or nicotine replacement, alcohol, and caffeine for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.

- To refrain from strenuous exercise, contact sports, and sunbathing for the 24 hours prior to all study site visits.

- To take their open-label metformin XR and their dose of double-blind study medication with time of dose noted on the eCRF if the patient is due for their weekly dose of double-blind study medication.

4.2.7 Day 63, Visit 12

Patients are to arrive at their study visit prior to 16:00 on Day 63. Study procedures will be performed as listed in Table 2. The IVRS/IWRS should be notified if the patient is discontinued from the study. The patient will obtain his or her fingerstick blood glucose level and input it to the CGM sensor as calibration points.

The CGM system sensor will be inserted, and confirmation that the system is working properly will be obtained. Patients will be sent home with instructions regarding calibration 2 hours after insertion, post dinner, before bedtime, and a fasting assessment the next morning, then calibrate every 12 hours (see Section 5.2.6.2). Patients should be reminded that the timing and content of meals should remain consistent across the 7-day CGM system monitoring period. See Section 3.8.1 for details on the meals. The SBGM measurements/records, and the calibration and function of the CGM system device should be reviewed.

In addition, patients should be reminded:

- Of the fasting requirements for the Day 64 visit (at least 8 hours prior to visit).

- To bring study medication and glucose meter to the next scheduled study visit.

- To call the investigative site if the fasting daily glucose on 3 consecutive days is ≥270 mg/dL (15 mmol/L).

- That the patient must re-calibrate the CGM system device every 12 hours per manufacturer's instructions.

- To bring study medication and glucose meter to the next scheduled study visit.

- To abstain from tobacco, nicotine or nicotine replacement, alcohol, and caffeine for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.

- The timing and content of meals should remain consistent across the 7-day CGM system monitoring period. See Section 3.8.1 for details.
- To refrain from strenuous exercise, contact sports, and sunbathing for the 24 hours prior to all study site visits.
- To take their open-label metformin XR and their dose of double-blind study medication with time of dose noted on the eCRF if the patient is due for their weekly dose of double-blind study medication.

Prior to the end of this visit, the patient will be scheduled to return on Day 64 (Week 10) for the standardized breakfast meal PPGT test, to occur between 06:00-10:00.

4.2.8 Day 64, Visit 13

Patients are to arrive at their study visit on Day 64 between 06:00-10:00. Study procedures will be performed as listed in Table 2.

The IVRS/IWRS should be notified if the patient is discontinued from the study. Patients will remain at the study site for collection of PK and biomarker blood samples according the sampling described below:

- Perform PK blood sampling prior to the meal (see Section 5.4).
- Collect blood samples for biomarker analysis prior to the meal (see Section 5.7).

Additionally, samples will be taken from patients for FPG, HbA1c, and safety laboratory assessments. See Table 4 for a list of the safety laboratory variables.

Patients will be provided a standardized breakfast following guidelines at the study site. The standardized breakfast meal should account for approximately 35% of the daily calorie intake (~700 kcal). The meal should be consumed in 30 minutes. These meals will remain consistent across the Day -7, 22, and Day 64 visits. For details on the procedures before and after the breakfast meal, see Section 5.3.1.

Patients will take their dose of double-blind study medication with time of dose noted on the eCRF if the patient is due for their weekly dose of double-blind study medication.

In addition, patients will be reminded:

- Of the fasting requirements for the Day 70 visit (at least 8 hours prior to visit).
- To call the investigative site if the fasting daily glucose on 3 consecutive days is ≥270 mg/dL (15 mmol/L).
- That the patient must re-calibrate the CGM system device every 12 hours per manufacturer's instructions.

- To bring study medication and glucose meter to the next scheduled study visit.
- To abstain from tobacco, nicotine, or nicotine replacement therapy alcohol, and caffeine for 24 hours prior to and during the study visits, which include the 24-hour glucose monitoring period.
- The timing and content of meals should remain consistent across the 7-day CGM system monitoring period. See Section 3.8.1 for details.
- To refrain from strenuous exercise, contact sports, and sunbathing for the 24 hours prior to all study site visits.

Prior to the end of this visit, the patient will be scheduled for the next study visit (Day 70 with 68, 69, and 70 window), to occur prior to 18:00.

4.2.9 Day 70, Visit 14

Patients are to arrive at their study visit prior to 18:00 on Day 70. Study procedures will be performed as listed in Table 2.

The IVRS/IWRS should be notified if the patient is discontinued from the study. Patients will remain at the study site for collection of PK and biomarker blood samples according the sampling described below:

- Perform PK blood sampling (see Section 5.4).
- Collect blood samples for biomarker analysis (see Section 5.7).

Additionally, samples will be taken from patients for FPG, HbA1c, and safety laboratory assessments. See Table 4 for a list of the safety laboratory variables.

At the conclusion of the CGM monitoring on Day 70, the CGM device will be removed.

All study medication will be collected, and the patient's compliance with study medication and open-label metformin XR based on pill count and with study medication (based on single dosing trays, returned kits, and drug accountability forms) will be assessed and recorded on the eCRF.

Prior to leaving the study site at the end of visit on Day 70, the patient will be scheduled for a 4-week follow-up visit.

Patients will be reminded about fasting requirements (at least 8 hours) prior to the follow-up visit.

4.3 Follow-up period

4.3.1 Safety follow-up visit, 4 weeks after Day 70 visit

Patients will arrive at the study site for a safety follow-up visit. Assessments for the follow-up visit are outlined in Table 2.

Samples will be taken from patients for safety laboratory assessments. See Table 4 for a list of the safety laboratory variables.

At this visit, IVRS/IWRS should be contacted to document study completion.

Note: other treatments during the 4 weeks of follow-up after Day 70 can be initiated.

4.4 Early termination visit

For patients who are discontinuing the study, the last study visit will serve as the early termination visit, with assessments as outlined in Table 2. The IVRS/IWRS should be contacted to discontinue the patient.

Blood samples for PK and biomarker analysis will be collected according the following schedule:

- Perform PK blood sampling, prior to the meal, if performed on a standardized breakfast meal PPGT test day (see Section 5.4).
- Collect blood samples for biomarker analysis, prior to the meal, if performed on a standardized breakfast meal PPGT test day (see Section 5.7).

Samples will be taken from patients for FPG, HbA1c, and safety laboratory assessments. See Table 4 for a list of the safety laboratory variables.

All study medication will be collected, and the patient's compliance with study medication and open-label metformin XR based on pill count and with study medication (based on single dosing trays, returned kits and drug accountability forms) will be assessed and recorded on the eCRF.

If the patient discontinues during one of the 7 day CGM periods, remove CGM device. The CGM device should not remain in place longer than 10 days.

If the patient is discontinuing the study due to an adverse event, a blood sample will be collected for assessment of exenatide plasma concentration.

Follow-up care for patients discontinuing the study should be discussed.

5. STUDY ASSESSMENTS

The electronic data capture (EDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Primary efficacy assessment

5.1.1.1 Mean weighted glucose

The primary efficacy assessment will be the 24-hour mean weighted glucose which will be estimated by dividing the area under the 24-hour glucose curve (AUC_{0-24}) by 24 hours and will be expressed in mg/dL. Detailed calculation will be defined in the statistical analysis plan (SAP). The glucose measurements used for assessment of the primary endpoint will be analyzed from the CGM data.

5.1.2 Secondary efficacy assessments

5.1.2.1 Postprandial glucose

Secondary assessments including the 2-hour mean weighted PPG and 2-hour PPG, (2 hours after the breakfast meal) will be obtained during blood draws for glucose measurements after the standardized breakfast during the onsite monitoring visits on Day -7, Day 22, and Day 64 (3 day window) and will be processed at the central laboratory. The 2-hour mean weighted PPG will be estimated by dividing the area under the 2-hour glucose curve by 2 hours. Detailed calculation will be defined in the SAP.

5.1.2.2 Mean daily glucose

The mean daily glucose will be calculated based on the CGM data from a 3 day window of CGM. Each of the mean daily glucose measurements and meals should be performed and recorded at approximately the same time during the 3 days prior to the 24-hour monitoring visit. It is important to keep the consistency and timing of meals similar.

5.1.2.3 Fasting plasma glucose

Secondary efficacy assessments include the central laboratory measurement of FPG at Screening, Day -7, Randomization (Day 1), Day 15, Day 22, Day 57, Day 64, Day 70, and Early Termination (ET).

5.1.2.4 HbA1c

Assessment of HbA1c will be measured using the central laboratory measurement of HbA1c at Screening, Randomization (Day 1), Day 15, Day 22, Day 57, Day 64, Day 70, and ET.

5.1.2.5 MAGE, and the proportion of time patients who had plasma glucose measurements <70 mg/dL, ≥70 mg/dL, and ≤180 mg/dL, and >180 mg/dL

Mean amplitude of glucose excursion, and the proportion of time patients who had plasma glucose measurements <70 mg/dL, ≥70 mg/dL, and ≤180 mg/dL, and >180 mg/dL will be measured using the CGM system device. Mean amplitude of glucose excursion is calculated for each patient by taking the arithmetic mean of blood glucose increases or decreases (from blood glucose nadirs to peaks or vice versa) when both ascending and descending segments exceed the value of 1 SD of the blood glucose concentration in a 24 hour period.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Standard clinical laboratory tests, blood pressures and heart rate will be taken at the times indicated in the Study Plan (see Table 2)

Table 4 presents the laboratory safety variables measured for this study.

Table 4 Laboratory safety variables

Hematology	Clinical Chemistry (serum)
Hemoglobin	Creatine kinase (creatine phosphokinase) (CK) (CPK)
Hematocrit	Total bilirubin
Red blood cell count	Alkaline phosphatase (ALP)
White blood cell count and differential	Aspartate transaminase (AST, SGOT)
Platelet count	Alanine transaminase (ALT, SGPT)
	Amylase
	Lipase
Urinalysis	Total protein albumin
pH, protein, glucose, leukocyte esterase, blood by dipstick	Electrolytes – sodium, potassium, chloride
Microscopy if dipstick positive for blood, leukocyte esterase or protein	Serum creatinine (Scr), calculated creatinine clearance (Cockroft-Gault formula)
Urine HCG pregnancy test for WOCBP (HCG minimum sensitivity of 25 IU/L)*	Blood urea nitrogen (BUN)

*Note: If a urine HCG test is positive, a blood specimen will be obtained and a serum pregnancy test will be performed by the central laboratory for confirmation.

Additionally, a serum beta-HCG pregnancy test will be performed if necessary.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. For information on how adverse events based on laboratory tests should be recorded and reported, see Section 6.3.

In case a patient shows an AST **or** ALT ≥3 × ULN **or** total bilirubin ≥2 × ULN please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

5.2.2 Physical examination

A complete physical examination will be performed on Day -28, Day 22, Day 64, and ET and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities), and neurological systems. A brief physical examination will be performed at Screening, Day -7, Day 1, Day 15, Day 57, Day 70, and at the follow-up visit and will include an assessment of the following: general appearance, sitting heart rate, sitting blood pressure, weight, and body temperature. Additionally the patient's chief complaints will be obtained during the physical examinations.

5.2.3 Height, weight, and body mass index

Measurement of weight should be performed with the patient dressed in indoor clothing, shoes removed, and bladder empty. Patients should be weighed on the same scale at all visits.

Measurement of height should be performed with the patient's shoes removed. The patient's knees should be straightened, head held erect, and eyes forward.

Body mass index is used as an index of obesity and is a method of defining normal body weight and excess body fat. It correlates in a population with percent body fat.

Body mass index is determined by weight (kg) divided by height (m) squared.

Method of BMI Calculation:

- Use actual height and weight to calculate BMI.
- To calculate BMI:
  - Convert pounds to kilograms (kg = lb / 2.2)
  - Convert inches to centimeters (cm = in × 2.54)
  - BMI = (weight in kg) / (height in cm/100)^2

Round to one decimal place (if .05 or greater, round up).

The BMI calculator provided by AstraZeneca may also be used to calculate BMI.

Additional calculations for BMI will be derived internally by AstraZeneca using the weight at the specified time point and the height at screening.

5.2.4 ECG

5.2.4.1 Resting 12-lead ECG

A standard resting 12-lead electrocardiogram (ECG) will be obtained at Day -28, Day 22, Day 64, Day 70, and ET. Electrocardiograms will be recorded after the patient has been lying down for 10 minutes. From the ECG, normal/abnormal/abnormal specifications and clinical significance of the abnormality will be recorded.

5.2.5 Vital signs

Vital signs consist of sitting pulse, sitting blood pressure, and temperature. Vital signs will be measured at Screening, Day -28, Day -7, Day -1, Day 1, Day 15, Day 22, Day 57, Day 64, Day 70, ET, and at the follow-up visit, after the patient has been seated for 5 minutes.

5.2.5.1 Pulse and blood pressure

Pulse will be determined while the patient is seated by palpation of the radial pulse for a period of 30 seconds and then multiplied by 2. Blood pressure will be measured while the patient is seated using a generally accepted cuff method, with an appropriately sized cuff. For timings of assessments, refer to Table 2.

5.2.5.2 Body temperature

Body temperature will be measured using an automated thermometer at the times indicated in Table 2.

5.2.6 Other safety assessments

5.2.6.1 Self-blood glucose monitoring

Patients will perform a fasting SBGM daily during the lead-in period. Fingersticks should be performed once daily after a minimum fast of 8 hours. If the FPG on 3 consecutive days is ≥270 mg/dL (15 mmol/L), the patient will be instructed to call the site. The site will review the glucose meter readings to confirm elevated glucose values. The patient will have a FPG performed by the central laboratory. If the FPG is ≥270 mg/dL (15 mmol/L), the patient will be considered for discontinuation from the study (see Section 3.9.1). If at the Day -7 visit, the patient has not performed fasting SBGM consistently and the central laboratory FPG ≥270 mg/dL, the patient should be considered for discontinuation.

On the Day -8 visit, the site should review the patient's CGM data to ensure that the patient performed the calibration correctly and followed appropriate guidance to ensure recording of

CGM data. Patients who experience suspected symptoms of hypoglycemia should perform SBGM and document the glucose measurement/reading at the time of the symptoms.

Glucose meters will be provided locally and will display in units of either mg/dL or mmol/L, as is the customary standard of practice in that country. All glycemic discontinuation criteria have been provided for each unit of measure.

If fingerstick glucose values are discordant from glycemic control assessed by the central laboratory or with clinical symptoms, the patient's glucose meter should be tested and the procedure for using it reviewed with the patient.

Supplies will be provided to allow for approximately 100 blood glucose assessments per month for the duration of the study. Patients should bring their glucose meter with them at each study visit to assure that it is functioning properly. Patients may keep the glucose meters at the end of the study.

5.2.6.2 Continuous glucose monitoring system

The CGM system measures the patient's interstitial glucose level using electrodes that measure an electric signal produced by glucose oxidase reaction. The system records data approximately every 5 minutes. The data will remain blinded to the patient during the recording and will be downloaded into a data file. The CGM system sensor will be inserted subcutaneously at the study site on Day -8, Day 21, and Day 63 at evening time prior to 18:00. Patients will be instructed on use of the glucose meter, the CGM system receiver, and calibration of the CGM system device according to the manufacturer's instructions. Patients will continue to wear the CGM system sensor and perform calibration according to manufacturer's instruction until the conclusion of 7-day glucose monitoring, or the 24-hour glucose monitoring period. The timing and content of meals should remain consistent across the 7-day CGM system monitoring period. See Section 3.8.1 for details on the meals. The CGM sensor will be removed at the study site at Day -1 (Week -1), Day 28 (Week 4), and Day 70 (Week 10).

The 7-day assessment using the CGM will be performed during the lead-in period (Day -8 to Day -1), and during the Treatment Period (Day 21 to Day 28 and Day 63 to Day 70). See Table 2 for additional details on when to insert and remove the device.

5.3 Other assessments

5.3.1 Procedures before and after the standardized breakfast meal

- The time of commencement of the breakfast meal on the day of the visit will be considered the 0 time point for all testing. Note: There is a window of ±2 minutes for sampling time points.

- At 60 minutes prior to the breakfast meal, confirm CGM system device is functioning properly.

- At 30 minutes prior to the breakfast meal, obtain blood specimens for glucose and standard safety assessments. Have the patient void urine (use this specimen for the urinalysis for the standard safety labs).
- On Day 22 and Day 64, perform PK blood sampling and biomarker analysis (prior to the breakfast meal).
- The time T1 = -30 will mark the beginning of the 24-hour blood glucose collection.
- Just prior to the breakfast meal, obtain blood specimens for glucose, insulin, glucagon, and C-peptide.
- The patient should consume the entire meal within 30 minutes. Note the time the meal was started and completed. Record on the eCRF.
- Obtain blood specimens for glucose, insulin, and c-peptide at 30, 60, 120, and 180 minutes following the breakfast meal.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Pharmacokinetic analyses will be conducted to explore the relationship between exenatide exposure (steady-state concentration) and glycemic response (weighted average AUC_{0-24}) on Day 64 and Day 70 of the Week 10 steady-state dosing interval. The PK samples collected on Day 64 and 70 of the dosing interval will be used to derive the steady-state exposure levels. Samples for PK assessments will be collected prior to the meal on Days 22 and 64. Directions for PK sample collection and processing will be provided in the central laboratory manual. The frequency of PK sampling is described in Table 2.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

5.4.2 Determination of drug concentration

Samples for determination of drug concentration will be analyzed by [redacted] on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Placebo samples are only conducted when there is cause to suspect administration of another study treatment. In such cases, a plasma sample, around the expected time of maximum plasma concentration, will be analyzed to confirm the presence or not of another study treatment.

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the clinical study report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AstraZeneca Biobank; see details in the Laboratory Manual).

5.5 Pharmacodynamics (Not applicable)

5.6 Pharmacogenetics (Not applicable)

5.7 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory. Collection the biological samples is an optional part of the study; the patient may continue in the study if they refuse consent for biomarker sampling.

Biological samples will be collected and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes, and toxicity.

Two additional blood samples (serum and plasma from 5 mL blood) will be collected on Day 1, Day 15, Day 22, Day 57, Day 64, Day 70, and ET and stored for the possible future analysis of biomarkers if allowed by local law. The results from other planned and on-going studies may warrant the investigation of specific biomarkers to better understand the mechanism of action and effects of exenatide in patients with type 2 diabetes or a better understanding of the patient at baseline. In addition, new biomarkers may be identified in the future that would provide additional information to understand this population. Biomarkers that may be investigated in the future from these samples may include:

- Antibodies to exenatide
- Biomarkers of inflammation and endothelial cell health, such as CRP, s-VCAM, or vWF
- Biomarkers of cardiovascular function
- Biomarkers of metabolism

5.7.1 Storage, re-use, and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. If these biomarkers are analyzed then the data will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.7.2 Labeling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

5.7.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their life cycle.

The Principal Investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca Biobank during the entire life cycle.

5.7.4 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG). In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term adverse event is used to include both serious and non-SAE.

6.2 Definitions of serious adverse event

An SAE is an adverse event occurring at any dose during any study period (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period.

Serious adverse events will be recorded from the time of informed consent up to 30 days after the last dose of study drug.

6.3.2 Follow-up of unresolved adverse events

Any adverse events that are unresolved at the patient's last adverse event assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing adverse event(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each adverse event:

- Adverse event (verbatim)
- The date when the adverse event started and stopped
- Maximum intensity
- Whether the adverse event is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- Whether the adverse event caused patient's withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date adverse event met criteria for an SAE
- Date Investigator became aware of an SAE
- Adverse event is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Description of adverse event.

Intensity rating scale:

1. Mild (awareness of sign or symptom, but easily tolerated)
2. Moderate (discomfort sufficient to cause interference with normal activities)
3. Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe adverse events. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An adverse event of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between investigational product and each adverse event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All adverse events spontaneously reported by the patient or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting adverse events, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and ECGs should therefore only be reported as adverse events if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product or if the Investigator, after consultation with the monitor, insists it should be reported as an adverse event.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an adverse event and the associated laboratory result/vital sign should be recorded on a laboratory/vital sign eCRF module which will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as adverse event(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an adverse event.

6.3.7 Hy's Law

Cases where a patient shows an AST or ALT ≥3 × ULN or total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction in cases of combined increase of aminotransferase and total bilirubin.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety Data Entry Site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an adverse event is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site personnel reports an SAE to the appropriate AstraZeneca representative by telephone, and the above timelines will apply.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

6.5 Overdose

An overdose is defined as a dose administered to a patient in excess of that specified in the AstraZeneca Core Data Sheet or Investigator's Brochure for that product unless specified otherwise in the Clinical Study Protocol.

- An overdose with associated adverse events is recorded as the adverse event diagnosis/symptoms on the relevant adverse event modules in the eCRF and on the Overdose eCRF module.

- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety Data Entry Site.

For overdoses associated with a SAE, i.e. fatal or life-threatening, the AstraZeneca representative ensures that the AstraZeneca Patient Safety Data Entry Site receives a report within one calendar day of initial receipt for all fatal or life-threatening cases.

For all cases that are not fatal or life-threatening, the AstraZeneca representative, in collaboration with the Investigator or other recipient of the data, actively obtains as complete a report as possible, such that the appropriate case report forms can be completed and submitted to the AstraZeneca Patient Safety Data Entry Site. The AstraZeneca representative ensures that the AstraZeneca Patient Safety Data Entry Site receives a report within 5 calendar days for all cases that are not fatal or life-threatening.

When an overdose is reported without associated adverse event (s), or an overdose with a non-SAE, the AstraZeneca representative sends the completed modules to the AstraZeneca Patient Safety Data Entry Site within 30 calendar days of initial notification of the overdose. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study the investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects, spontaneous miscarriages, or ectopic pregnancy should be reported and handled as SAEs. Elective abortions without complications should not be handled as adverse events. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

If the serious criteria are met for fatal or life-threatening, then The AstraZeneca representative confirms that a congenital abnormality/birth defect, spontaneous miscarriage, or ectopic pregnancy has occurred, which meets the criteria for definition as a SAE (fatal or life-threatening) then the AstraZeneca representative ensures that the AstraZeneca Patient Safety Data Entry Site receives a report within 1 calendar day of initial notification for all fatal or life-threatening cases. For all cases that are not fatal or life-threatening the AstraZeneca representative ensures that the AstraZeneca Patient Safety Data Entry Site receives a report within 5 calendar days of initial notification. If the outcome of the pregnancy is a normal birth or elective abortion then the AstraZeneca representative ensures that the AstraZeneca Patient Safety Data Entry Site receives a report within 30 calendar days of notification following a normal birth or elective abortion.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Time period for restricting procreation after end of study is set at ×5 half-lives plus 2 weeks.

Male patients should refrain from fathering a child or donating sperm during the study and for 30 days following the last dose.

6.7 Management of IP related toxicities

Dose reductions of the study medication are not permitted in this study.

6.8 Study governance and oversight (Not applicable)

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

All study drugs will be provided to the sites by AstraZeneca.

All IPs will be packed into kits containing enough IP for 4 weeks of treatment. The vials contained exenatide/placebo powder for injections will be packed into a small box containing 4 vials. Four syringes with dilutent for suspension of EQW and matching placebo will be packed into another box also containing 6 vial adapters and six 23-gauge × 5/16 inch needles.

Metformin will be supplied via pharmacy cards through a pharmacy.

If a patient is on 1500 mg of metformin XR at screening, they will receive 1500 mg metformin XR during the lead-in period. If a patient is on 2000 mg of metformin XR at screening, they will receive 2000 mg metformin XR during the lead-in period. Patients on 2500 mg or 2550 mg of metformin XR daily (850 mg TID) will receive 2000 mg of metformin XR.

Study drugs will only be dispensed to patients in accordance with the protocol. Table 5 presents the investigational products used in this study.

Table 5 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer
Exenatide once weekly (EQW)	2.0 powder for injection	AstraZeneca
Placebo to match exenatide once weekly	Placebo powder for injection	AstraZeneca

7.2 Dose and treatment regimens

Double-blind study medication will be administered subcutaneously once weekly (Day 7 each week). The IVRS/IWRS, described in Section 3.5, will be used to assign each patient EQW or placebo, at the appropriate dispensing visits.

Patients will take their first dose of double-blind study medication (EWQ or placebo) at the site on Day 1. The time of first dose will be noted on the eCRF. Patients will be trained on IP administration at this visit. The injection must be administered immediately after preparation of the dose.

During the treatment period, patients will take the double-blind study medication once weekly (Day 7 each week). Patients will take metformin XR once daily with the evening meal.

The study design includes the following 2 treatment periods:

Medical nutrition and metformin XR lead-in period

After qualifying for entry into the lead-in period, patients will discontinue their current metformin therapy and begin a 4-week, medical nutrition, and open-label metformin XR lead-in period. Patients will be given pharmacy cards to obtain metformin XR. The dose of metformin XR assigned will correspond with each patient's background dose of metformin. Each patient will be instructed to take:

- Open-label metformin XR: 3-4 tablets with the evening meal (1500-2000 mg)

Compliance with the administration of multiple tablets will be assessed during the lead-in period. Patients must demonstrate good compliance (see Section 7.5) with metformin XR (80% to 120%) during the lead-in period and the ability to have a week-long CGM measurement to be eligible for randomization.

Double-blind treatment period

Following completion of the lead-in period, eligible patients will enter the 10-week, double-blind treatment period.

Patients will be randomized to 1 of 2 treatment arms:

- EQW + open-label metformin XR (1500-2000 mg).
- Placebo + open-label metformin XR (1500-2000 mg).

The double-blind study medication (either EQW or placebo) will be administered subcutaneously once weekly and the metformin XR will be taken once daily with the evening meal.

7.3 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the study medication kit specifies the appropriate storage.

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF.

Each time study medication is dispensed, compliance will be reinforced. When study medication is returned, compliance will be assessed based on an interview with the patient and a count of the tablets of metformin XR returned which should be between 80% to 120% of that prescribed. During the treatment period, compliance with EQW will be assessed by reviewing the used vials. Patients will be asked to bring their used vials into the site visit. The Investigator (or designee) will record the amounts of study medication dispensed and returned at each visit and the dates of any study drug interruption. If the patient is not between 80% to 120% compliant with open-label metformin XR during the lead-in period, the patient will not be eligible for randomization. If the patient is not between 80% to 120% compliant during the double-blind treatment period, the period of noncompliance should be noted as a protocol deviation and AstraZeneca should be notified. The patient should be educated regarding the schedule for taking study drug.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

For this study, study drugs (those supplied by AstraZeneca or sourced by the Investigator) such as partially used study drug containers, vials, and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible AstraZeneca Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to AstraZeneca upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for destruction of study drug.

It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

7.7 Concomitant and other treatments

Patients will be allowed to use any other concomitant medications they require during the study except: systemic glucocorticoid therapy of greater than 14 consecutive days' duration (with the exception of topical, intraocular, and inhaled preparations).

Patients will not be allowed to use acetaminophen or paracetamol during the study, as these two drugs may interfere with the CGM device.

Patients will continue metformin XR during the study. Patients should discontinue other oral anti-hyperglycemic mediations at least 4 weeks prior to screening. The intent of this study is that patients do not deviate from their metformin regimen. However, in emergencies, it may be necessary for patients to change their dose of metformin XR. This is allowed for up to 7 consecutive days or up to 7 days within a month. If such a situation occurs more than once during the study or lasts longer than 7 consecutive days or more than 7 days within a month, a decision to keep the patient in the study should be made only after consultation between the Investigator and the AstraZeneca clinical research physician. The decision should be documented by a note to the Investigator's file.

Patients must follow the medication restrictions outlined in the inclusion and exclusion criteria (Section 3.1 and Section 3.2, respectively) during the study. Dosages for certain concomitant medications should remain constant during the study unless instructed otherwise by the Investigator or treating physician. Any change in regimen for any concomitant medication, including restricted concomitant medications, must be reported to the Sponsor.

Table 6 lists the prohibited medications and the applicable time frames for this study.

Table 6 Restricted medications

Restricted medication/class of drug	Usage
Anti-hypertensive agents	Patient must either not be treated with or has been on a stable treatment regimen for a minimum of 2 months prior to Screening.
Thyroid replacement therapy	Patient must either not be treated with or has been on a stable treatment regimen for a minimum of 2 months prior to Screening.
Anti-depressant agents	Patient must either not be treated with or has been on a stable treatment regimen for a minimum of 2 months prior to Screening.
Exenatide (including Byetta®, Bydureon™, or exenatide suspension) or any GLP-1 analog	Exposure 6 months prior to Screening is prohibited (or use of non-study products during the study).
Dapagliflozin (FORXIGA, FARXIGA) or any SGLT-2 inhibitor	Exposure 8 weeks prior to Screening is prohibited (or use of non-study products during the study).
Thiazolidinedione	Exposure 12 weeks prior to Screening is prohibited.
Any DPP-4 inhibitor	Prohibited 12 weeks prior to Screening and during the study.
Pramlintide (SYMLIN®)	Prohibited within 3 months prior to Screening and during the study.

Table 6 Restricted medications (Continued)

Restricted medication/class of drug	Usage
Systemic corticosteroids by oral, intravenous, intra-articular, or intramuscular route	Patient must not have received either repeated acute intermittent corticosteroid treatment or non-replacement corticosteroid therapy for longer than 7 consecutive days during the 4 weeks prior to Screening. Stable replacement corticosteroid treatment administered for at least 4 weeks prior to Screening is allowed.
Potent, inhaled, or intrapulmonary (including ADVAIR®) steroids known to have a high rate of systemic absorption beclomethasone dipropionate nasal and oral inhalation (Beclovent, Beconase, Qnasl, QVAR) budesonide nasal and oral inhalation (Pulmicort, Symbicort, Rhinocort) flunisolide oral inhalation aerosol and nasal route (AeroBid, Aerospan, Nasalide, Nasarel) fluticasone propionate aerosol and powder (Advair, Flovent) mometasone furoate aerosol and powder inhalation (Asmanex, Dulera)	Prohibited within 3 months prior to Screening and during the study.
Prescription or over-the-counter weight loss medications	Prohibited within 3 months prior to Screening and during the study.

Note: This is not a comprehensive listing. If the exclusion status of any concomitant medication is in question, please contact the medical monitor for discussion. The following steroids are permitted during the study: ciclesonide oral inhalation and nasal spray (Alvesco, Omnaris, and Zetonna).

7.7.1 Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.8 Post study access to study treatment

At the end of the study, AstraZeneca will not continue to supply study drug to patients/investigators unless AstraZeneca chooses to extend the study. The Investigator should ensure that the patient receives appropriate standard of care to treat the condition under study.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.

8.2 Sample size estimate

Approximately 110 patients are expected to be randomized 1:1 to the EQW + metformin XR and placebo + metformin XR treatment arms (55 patients per treatment arm). The assumed dropout rate (30%) was based on a similar study (SHOT study; 20%), and increased by 10% as the present study is of longer duration, with a more demanding visit schedule. Therefore, a minimum of 39 patients per treatment arm would provide the necessary statistical power.

With 39 patients per treatment group, there is a 90% power to detect a difference in change in 24-hour mean weighted glucose of 18 mg/dL at Week 4 between exenatide once weekly and placebo, assuming an SD of 24 mg/dL. As the plasma exenatide concentrations are expected to continuously increase and achieve steady-state around Week 7-8, the treatment effect on glycemic control will be increased, therefore, it is expected that 39 patients per treatment group will provide >90% power for the Week 10 treatment comparison. With this sample size, there is approximately 83% power to detect a treatment difference in change in FPG of 30 mg/dL, assuming an SD of 45 mg/dL, and approximately 80% power to detect a difference in change in 24-hour mean weighted glucose of 32 mg/dL between treatments, assuming an SD of 50 mg/dL.

The above power calculation is based on a 2-sided t-test at α=0.05. Family-wise Type I error will be controlled at 0.05 for primary and secondary endpoints by applying a sequential testing process. The hierarchical order is defined in Section 8.5.2.

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis sets

The Modified Intent-to-Treat (ITT) population will consist of all randomized patients who received at least one dose of randomized study drug. The Modified ITT population will be used for all efficacy analyses.

The Evaluable population will consist of all Modified ITT patients who completed the study and were in compliance of study procedures. The Evaluable population will be used to perform supportive analyses for primary and secondary endpoints.

8.4 Outcome measures for analyses

8.4.1 Primary endpoint

The primary endpoint for this study is the change in 24-hour mean weighted glucose from baseline (Day -1/1) to Day 6 of Week 10 (Day 69/70) and to Day 6 of Week 4 (Day 27/28).

Note: Day 6 data will consist of data from Day 6 ±1 day (Days 5 through 7).

There will also be an average of change in 24-hour mean weighted glucose from baseline to Days 1 to 6 of Week 10 and Week 4 calculated (SD, MAGE, "Distance travel", "Energy").

8.4.2 Secondary endpoints

The secondary endpoints for this study are the following:

- Change in 24-hour mean weighted glucose between Day 1 of Week 10 (Day 64/65) and Day 6 of Week 10 (Day 69/70) within each EQW-treated patient
  - Note that Day 6 data will consist of data from Day 6 ±1 day (Days 5 through 7)
  - There will also be an average of change in 24-hour mean weighted glucose from baseline to Days 1 to 6 of Week 10 and Week 4 calculated (SD, MAGE, "Distance travel", "Energy")
- Change from baseline (Day 1) to Day 6 of Week 10 (Day 70) and Day 6 of Week 4 (Day 28) in FPG
- Change from baseline (Day -1) to Day 6 of Week 10 (Day 69) and Day 6 of Week 4 (Day 27) in 2-hour mean weighted PPG (after the breakfast meal)

8.4.3 Exploratory endpoints

The exploratory endpoints for this study are the following:

- Change from baseline (Day -1/1) to Week 10 (Day 69/70) and Week 4 (Day 27/28) in the 24-hour MAGE using CGM system
- Change from baseline (Day -1/1) to Week 10 (Day 69/70) and Week 4 (Day 27/28) using CGM system, in the proportion of time patients who had plasma glucose measurements <70 mg/dL
- Change from baseline (Day -1/1) to Week 10 (Day 69/70) and Week 4 (Day 27/28) using CGM system, in the proportion of time patients who had plasma glucose measurements ≥70 mg/dL and ≤180 mg/dL
- Change from baseline (Day -1/1) to Week 10 (Day 69/70) and Week 4 (Day 27/28) using CGM system in the proportion of time patients who had plasma glucose measurements >180 mg/dL
- Change from baseline (Day 1) to Week 10 (Day 70) and Week 4 (Day 28) in HbA1c

- Change from baseline (Day -1) to Day 6 of Week 10 (Day 69) and Day 6 of Week 4 (Day 27) in 2-hour PPG (after the breakfast meal)

- Differences between mean daily 24-hour glucose profile during 7-day CGM system assessments during the lead-in period and 7-day CGM system assessments during Week 10.

  – Additionally, the relationship between exenatide exposure (steady-state concentration) and glycemic response (weighted average AUC_{0-24}) on Day 64 and Day 69 of the Week 10 steady-state dosing interval will be explored (SD, MAGE, "Distance travel", "Energy")

8.5 Methods for statistical analyses

Analysis of data will be performed after all patients have completed or have been discontinued from the study. In addition, all relevant queries must be answered and the database must be locked 30 days, prior to the analysis.

8.5.1 Analysis of the primary variable(s)

The primary endpoint of 24-hour mean weighted glucose will be obtained by a CGM method and calculated as the AUC from the 24-hour glucose profile, divided by 24 hours. Details on AUC computations for partially missing 24-hour glucose profiles will be described in the SAP. The changes in 24-hour mean weighted glucose from baseline (Day -1/1) to Day 5-6 of Week 10 (Day 69/70) and to Day 6 of Week 4 (Day 27/28) will be analyzed using a maximum likelihood-based mixed model repeated measures (MMRM) method. The MMRM model will include change in 24-hour mean weighted glucose as the dependent variable; treatment, HbA1c stratum (<8.5% vs. ≥8.5%), baseline 24-hour mean weighted glucose, week of visit, and treatment-by-week interaction as fixed effects, and patient and error as random effects. All post-baseline measurements (including early termination visits) of the 24-hour mean weighted glucose will be included in the analysis with no imputation of missing data other than that inherent in the MMRM model. An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion. The least squares (LS) means, standard errors of LS means, and 2-sided 95% confidence intervals (CI) for the mean change within each treatment group and the difference between treatment groups will be presented. P-values will be provided for the comparison between treatment groups. Data normality will be evaluated. If the data require logarithm transformation to meet the normality assumption for statistical modeling, the LS mean and the corresponding 95% CI will be calculated at the log scale, and the geometric mean ratio and its corresponding 95% CI will be calculated by taking the anti-log of the corresponding values within each treatment group and for treatment comparisons. The 2 primary endpoints will be tested sequentially (Week 10 comparison will follow by the Week 4 comparison) and the family-wise Type I error will be controlled between primary and secondary endpoints. See description in Section 8.5.2.

8.5.2 Analysis of the secondary variable(s)

Intra-patient difference and variability of the 24-hour weighted mean glucose between Day 1 and Day 6 of Week 10 will be calculated and presented descriptively; no hypothesis testing will be performed.

The change in FPG from baseline (Day 1) to Day 6 of Week 10 (Day 70) and Day 6 of Week 4 (Day 28), and the change in 2-hour mean weighted PPG (after the breakfast meal) from baseline (Day -1) to Day 6 of Week 10 (Day 69) and Day 6 of Week 4 (Day 27) will be analyzed using a similar MMRM model as the one described for the primary endpoints; except for the analysis of the endpoint of FPG, the baseline FPG will replace the baseline 24-hour mean weighted glucose as one of the fixed effects.

The change in HbA1c from baseline (Day 1) to Day 6 of Week 10 (Day 70) will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline HbA1c as a covariate.

In order to control the family-wise Type I error, a sequential testing procedure will be implemented. In the hierarchical testing order, the primary endpoints of 24-hour mean weighted glucose at Week 10 will be tested first, followed by 24-hour mean weighted glucose at Week 4, then the secondary endpoints: FPG at Week 10, 4-hour mean weighted glucose at Week 10, then FPG at Week 4, and 4-hour mean weighted glucose at Week 4.

8.5.3 Analysis of the exploratory variable(s)

The MAGE will be calculated for each patient by taking the arithmetic mean of blood glucose increases or decreases (from blood glucose nadirs to peaks or vice versa) when both ascending and descending segments exceed the value of 1 SD of the blood glucose concentration in a 24 hour period. The proportion of time that patients had plasma glucose measurements <70 mg/dL, ≥ 70 mg/dL and ≤ 180 mg/dL, and >180 mg/dL will be calculated as the time period the glucose level falls into the pre-specified criteria, divided by the total time period. Detailed calculation will be described in the SAP.

Tertiary endpoints will be analyzed using a similar MMRM model to the primary and secondary endpoints, with the baseline value of the dependent variable included as a fixed effect factor.

Daily 24-hour glucose profile collected during the 1 week lead-in period and during Week 10 will be summarized descriptively and plotted. The difference and/or similarity will be discussed.

8.5.4 Interim analysis

An interim analysis with the objective of determining enrollment targets for the remainder of the study may be performed at the Study Director's discretion at approximately the time when the 30th patient from each study arm completes the 10-week visit with the primary efficacy evaluation. The actual timing of the interim analysis will be determined by the Study Director

and will depend on the observed enrollment rates and the distribution of enrollment over the study sites. An unblinded statistician independent of the study conduct will perform the interim analysis and communicate the results to a Study Director designated committee that will make necessary decisions and communicate those to the study team for implementation.

The focus of this interim analysis will be the population mean treatment difference, treatment minus placebo, in the change from baseline for the 24-hour mean glucose as measured by the patient CGM devices, at the Week 10 visit (using the definition of the primary endpoint as defined in Section 8.4.1). The data used for this analysis will come from the patient's 24 hour mean evaluations at both the 4-week and the 10-week visits, and patients having only a 4-week visit will be included in this analysis. The model used for the evaluation of the population mean 10-week treatment difference will assess the relationship of the Week 4 and Week 10 results in order to achieve greater precision for the Week 10 decision.

A Bayesian methodology will be used to project the eventual success at the planned final analysis (statistical significance at $p = 0.05$ two-tailed) as described in Section 8.4.1 of the study protocol. The model will utilize a bivariate normal-Wishart conjugate prior assuming very little information regarding the population treatment differences and population error covariance matrix, and will eventually lead to a posterior distribution of the population Week 10 mean treatment difference conditioned on the interim observed mean differences at Weeks 4 and 10, and the observed error covariance matrix (Week 4 variance, Week 10 variance, Week (4, 10) covariance). From this posterior distribution, the predicted power of the final primary efficacy comparison at the planned final sample size will be calculated by computing the conditional power at a fixed population mean Week 10 difference given the results of the interim analysis, then averaging over all population mean differences using the posterior distribution obtained from the interim analysis. This is the interim average power of final success at the original planned sample size given the interim results, and decisions will be based on this interim average power.

The decision criterion will have the following form:

a. Curtail enrollment (stop enrollment), continue all currently enrolled patients to their final visit and perform the final analysis on the reduced set of patients (at $p = 0.05$ two-tailed). This decision will occur under either of the 2 following interim analysis results, but only the higher level decision to stop further enrollment not which of the underlying conditions that has been met will be communicated to the Study Director designated committee and the study team.

    - (Early futility) if the interim average power is less than 20%, or
    - (Early efficacy) the interim average power is greater than 90%.

b. Continue Enrollment. If the interim average power is greater than or equal to the early futility boundary of 20%, and less than or equal to the early efficacy boundary of 90%, then at the Study Director designated committee's discretion the study will either:

   - Continue to its planned final sample size and perform the final 10-week treatment comparison as originally planned (at p = 0.05, two-tailed), or

   - Continue with a potentially updated enrollment target. The unblinded statistician will provide the interim sample sizes and an updated average power for the trial given the interim results to guide decision making about an updated enrollment target for the study. In this case, any other decision outside the scope of the criteria above an appropriate adjustment will be determined by the unblinded statistician to preserve the overall p-value inherent with this decision using a Lan-Demets methodology.

Further details of the methodology will be described in the SAP.

8.5.5 Safety analysis

The number and percent of patients with an adverse event will be summarized for each treatment group. Changes from baseline to each scheduled visit for each clinical laboratory test, blood pressure and heart rate will be summarized by treatment group. In addition, the number and percent of patients with a predefined marked abnormality, using standard definitions, in clinical laboratory tests will be summarized by treatment group. Electrocardiogram data will be summarized.

8.5.6 Biomarker analysis

No biomarker analysis is planned at this time.

8.5.7 Demographic and baseline characteristics

Demographic and baseline characteristics will be summarized by treatment group as well as for all patients combined. Baseline is defined as the last measurement prior to the first randomized dose of double-blind medication. No statistical test will be carried out for comparison of any baseline measurement between the treatment groups.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and EDC system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient
- The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center need information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The Principal Investigator at the center(s) should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study or any resulting publications. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of the Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in the 4th quarter 2014 and to end by 4th quarter 2015.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with BYDUREON.

9.4 Data management by Medpace

Data management will be performed by Medpace, according to the Data Management Plan. The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by Medpace.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation

(ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An institutional review board (IRB) should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The opinion of the IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, the IRB, and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study

- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the Informed Consent Form that is approved by an IRB

10.5 Changes to the protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRB see Section 10.3.

If a protocol amendment requires a change to a center's Informed Consent Form, AstraZeneca and the center's IRB are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded,

analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

11. LIST OF REFERENCES

American Diabetes Association, 2014
American Diabetes Association. Standards of medical care in diabetes- 2014. Diabetes Care 2014; 37:S14-S80.

Bolen et al, 2007
Bolen S, Wilson L, Vassy J, Feldman L, Yeh J, Marinopoulos S, Wilson R, Cheng D, Wiley C, Selvin E, Malaka D, Akpala C, Brancati F, Bass E. Comparative effectiveness and safety of oral diabetes medications for adults with Type 2 diabetes. Rockville, MD: Agency for Healthcare Research and Quality, Department of Health and Human Services (US); July 2007. Comparative Effectiveness Review No. 8. (Prepared by the Johns Hopkins Evidence-based Practice Center under Contract No. 290-02-0018).

AstraZeneca Pharmaceuticals LP, 2014
AstraZeneca Pharmaceuticals LP. Exenatide Injections Investigator Brochure (Version 3). Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2014.

BYDUREON, 2014
BYDUREON® (exenatide extended-release for injectable suspension) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2014.

BYETTA, 2014
BYETTA® exenatide injection [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2014.

Centers for Disease Control and Prevention, 2014
Centers for Disease Control and Prevention. Diabetes Latest [Internet]. Year [cited date 17 June 2014]. Available from: http://www.cdc.gov/features/diabetesfactsheet/.

Ceriello, 2008
Ceriello A, Colagiuri S. International Diabetes Federation guideline for management of post meal glucose: a review of recommendations. Diabet Med 2008; 25:1151-1156.

Cervera et al, 2008
Cervera A, Wajcberg E, Sriwijitkamol A, Fernandez M, Zuo P, Triplitt C, Musi N, DeFronzo RA, Cersosimo E. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. Am J Physiol Endocrinol Metab. 2008;294(5):E846-52.

Drucker et al, 2008
Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, Porter L. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomized, open-label, non-inferiority study. Lancet. 2008;372(9645): 1240-50.

Fehse et al, 2005
Fehse F, Trautmann M, Holst JJ, Halseth AE, Nanayakkara N, Nielsen LL, Fineman MS, Kim DD, Nauck MA. Exenatide augments first- and second-phase insulin secretion in response to intravenous glucose in patients with type 2 diabetes. J Clin Endocrinol Metab. 2005;90(11):5991-7.

Kieffer et al, 1995
Kieffer TJ, McIntosh CH, Pederson RA. Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-like peptide 1 in vitro and in vivo by dipeptidyl peptidase IV. Endocrinology. 1995;136(8):3585-96.

Kolterman et al, 2003
Kolterman OG, Buse JB, Fineman MS, Gaines E, Heintz S, Bicsak TA, Taylor K, Kim D, Aisporna M, Wang Y, Baron AD. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in patients with type 2 diabetes. J Clin Endocrinol Metab. 2003;88(7):3082-9.

Miser, 2007
Miser W. The Management of Type 2 Diabetes Mellitus FOCUS on Quality. Prim Care Clin Office Pract. 2007;34:1-38. 34, 1-38.

Monnier, 2003
Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variation with increasing levels of HBA1c. Diabetes Care 2003; 26:881-885.

Monnier, 2007
Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabetes Care 2007; 30:263-269.

Rodbard, 2007
Rodbard HW, Blonde L, Braithwaite SS et al, AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 2007; 13 (Suppl. 1):1-68.

Woerle, 2007
Woerle HJ, Neurmann C, Zschau S et al. Impact of fasting and postprandial glycemic control in type 2 diabetes: importance of postprandial glycemia to achieve target HbA1c levels. Diabetes Res Clin Pract 2007; 77: 280-285.

Clinical Study Protocol Appendix B

Drug Substance	Exenatide
Study Code	D5551L00006
Edition Number	1.0
[redacted]	[redacted]

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the adverse event as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an adverse event occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered adverse events if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an adverse event may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the adverse event occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the adverse event consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the adverse event be anticipated from its pharmacological properties?

- De-challenge experience. Did the adverse event resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The adverse event cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the adverse event reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	Exenatide
Study Code	D5551L00006
Edition Number	1.0
[redacted]	[redacted]

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

AstraZeneca

Clinical Study Protocol Appendix D

Drug Substance	Exenatide
Study Code	D5551L00006
Edition Number	1.0
[redacted]	[redacted]

Appendix D
Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 6.3.7 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events and serious adverse events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3 × Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥2 × ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3 × ULN **together with** TBL ≥2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN
- AST ≥3 × ULN
- TBL ≥2 × ULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.
- Complete the 3 Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an adverse event will be made and subsequently whether the adverse event meets the criteria for a SAE:

- If the alternative explanation is **not** an adverse event, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an adverse event/SAE, record the adverse event/SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf